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ARCHIVES OF SURGERY

VOLUME 27 JULY, 1933 NUMBER 1

# PHYSIOLOGY OF THE COLON

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The large intestine in most animals, including man, is generally regarded as possessing merely storage function similar to that of a catch basin so that defecation may take place at a convenient time. In other words, it is looked on as a fixed tube, or system of tubing, present mainly to transmit feces. Metchnikoff's claim that man at one time made use of his large intestine as a reservoir, enabling him to pursue his prey or run away from enemies without undergoing risk of stopping to evacuate the bowels, no doubt contains much truth. However, his belief that people can live without this portion of the intestine, and that of Lane,[1] Waugh [2] and others regarding intestinal stasis and other possible evils for which the colon can be responsible, have thrown this organ into disrepute and probably have discouraged extensive study of its physiology. It is true that individuals can live without the large intestine; that certainly is no proof of its uselessness. On the other hand, it is no doubt true that this organ is undergoing a process of evolution better to suit changing needs and fashions, a fact which especially emphasizes itself in a consideration of present-day dietary standards. Under the conditions of living in the twentieth century, it is true that in certain instances the colon can be removed and not be missed, yet that does not prove that it is of no significance in human economy. It also may be possible that the organ has outlived its usefulness in the process of development of the body, but there can be no doubt that in lower animals its functions are definite and its loss is attended with serious results. However, in man, although to less extent, possibly, it has been proved that the colon can be removed without injury,

Abridgment of a thesis submitted by Dr. Larson to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery. Work done in Division of Experimental Medicine, the Mayo Clinic.

1. Lane, W. A.: The Operative Treatment of Chronic Intestinal Stasis, ed. 4, London, Henry Frowde, 1918.

2. Waugh, G. E.: The Morbid Consequences of a Mobile Ascending Colon, with a Record of 180 Operations, Brit. J. Surg. **7**:343 (Jan.) 1920.

and there is no question as to the advisability of colectomy in such conditions as multiple diffuse polyposis.

From a study of the physiology of the large intestine it may be concluded that it is a bifunctional organ and, indeed, when one considers its embryologic development such a conclusion is obvious. Beginning low in the pelvis in the embryo and ascending upward in the median line, or slightly to the left, in the early months of fetal life the colon is a left-sided organ up to the splenic flexure, and it remains so in after-life, held in place by peritoneal fusion. From the splenic flexure, it festoons itself across the abdomen to another fixed point under the liver, arriving there at about the third or fourth month, whence it extends to the right iliac fossa to a semifixed situation in adults. This rotation around the superior mesenteric vessels is counterclockwise and constant, except in a small number of variants. In addition, the left half of the colon is developed from the hindgut, whereas on the opposite side it takes its origin with the small bowel below the papilla of Vater from the midgut, or the absorptive portion of the gastro-intestinal tract. This embryologic difference and the development of the proximal portion of the colon with the small bowel early called attention to the fact that there must be dissimilarity of physiologic function in the two halves, and the normal association of the proximal portion of the colon with the small bowel from the standpoint of physiology was readily established. Anatomic differences in conformation and construction in the two halves likewise indicated a difference of purpose. When pathologic processes developed, a study of them indicated that different types of lesions were found as a routine in the two arms of the colon, producing different symptoms. For example, a malignant lesion of the right side of the colon clinically called attention to itself by disturbances of the physiologic equilibrium, in sharp contradistinction to the obstructive phenomena characteristic of the distal part of the colon.

The cecum has long been regarded as a second stomach of primary significance in digestion and absorption, especially regarding cellulose in the herbivora; likewise, its enormous variation in size and appearance in various animals has been a subject of comment by many authors. It is regarded as of much shorter heredity than the small bowel and with a function which has been changing in the process of its evolution, so that definite statements regarding the physiology of this portion of the bowel cannot be made which hold true in all instances. In general, it may be stated, however, that the function of the right half of the colon is an absorptive one and that its movements are so regulated that progress of the food is slowed and thorough mixing is assured, thus favoring absorption. In the human being, very little digestion takes place here, although in some herbivora, especially in the horse, there is evidence that considerable takes place. The left portion of the large

intestine has a longer heredity; its functions are likewise more fixed, and in most animals it has been established that this portion acts more or less as a magazine for storage of residue. In general, the contents here are hard and more or less incompressible, whereas those of the right portion of the colon are semiliquid, so a rough division of the functional behavior may be made on this point alone. The mechanical activity of the two portions bears this out as the most distal part acts as a duct through which the contents are evacuated. It is thus seen that primarily the function here is propulsion and expulsion. Besides the motor and absorptive functions, the physiology of the colon includes that of secretion and excretion, the latter being no less important than the others and no doubt linked up with the elimination of poisons and toxins, as well as with the formation of the normal secretions of the colon.

## MOVEMENTS OF THE PROXIMAL PORTION

The movements of the large intestine have been investigated by many writers, yet there are many points which still remain unsolved. Researches in this field have been conducted from many angles of approach, such as by the use of an abdominal window, by isolated strips of bowel, by observing the effect of section of nerves, by the use of various diets, by the action of drugs and by the use of pressure methods, such as balloons, and in recent years the use of the roentgen ray with a contrast medium has been invaluable in the study of the physiology of the colon.

After the introduction of roentgenoscopic methods in 1896, attention was drawn to many misconceptions in the field of gastro-enterology and, in a great number of cases, conditions which had formerly been considered anatomic variations were found instead to be normal physiologic movements; consequently, numerous revisions of the concepts of functions of the small and large intestines were necessary.

The first extensive study of the movements of the large bowel seems to have been made by Cannon [3] in 1902, who, by means of the roentgen ray, traced an opaque meal consisting of bismuth subnitrate mixed with salmon through the alimentary tract of the cat. Valuable deductions were made. In the cecum of the animal he found the most common movements to be antiperistalsis, as contrasted to the tonic rings of contraction and propulsive waves in the descending portion of the colon. These waves, he noticed, followed one another like those of the stomach, beginning either at the more advanced portion of the content in the colon or at the nearest tonic constriction, which he observed was frequently found at the termination of the transverse segment of the colon.

3. Cannon, W. B.: The Movements of the Intestines Studied by Means of the Röntgen Rays, Am. J. Physiol. **6**:251 (Jan.) 1902.

The first sign of activity was an irregular undulation of the walls of the organ; then faint constrictions passed backward to the cecum. They usually appeared at first only in the region of the ascending colon, but often started near the end of the transverse segment and passed without interruption to the tip of the cecum, where new waves of peristalsis were inaugurated, and these waves finally succeeded in carrying food to the distal transverse colon. The activity was periodic with gradual disappearance of movements in a manner similar to that in which they appeared. Such a period of antiperistalsis lasted usually from four to five minutes and it was repeated at varying intervals, often from three to six times an hour. About twenty-five waves affected any one particle of food so that the result was a thorough mixing of contents, favoring close contact with the absorbing surfaces. These waves in the proximal part of the colon were definitely influenced by psychic factors. Cannon [3] inhibited these movements by holding the cat's nose so it could not breathe, and this in time stopped the movements altogether. There was no cessation of contractions during sleep; likewise, the movements continued during the night. Jacobj,[4] in 1890, seems to have been the first to recognize antiperistaltic movements in the colon, and although he did not describe them in detail, he did state that they seemed to originate from a more or less broad constriction ring. He used cats in which he produced colchicum poisoning, and his studies were made primarily on the small bowel.

Elliott and Barclay-Smith,[5] in a thorough study of antiperistalsis, using etherized animals under saline baths and injecting pea soup into the segments of bowel studied, made observations which in general agreed with those of Cannon. They also classified the different movements of the colon in a manner to explain the varying morphologic differences of that part of the alimentary tube in various mammals. Such difference, they stated, is related to habits of diet and not necessarily to zoologic classification. In the cat they found antiperistalsis, or backward-running waves of constriction, inherent throughout the length of the colon, and not confined to its proximal portion; yet, as a rule, this regressive movement was rarely present except in the ascending, transverse and cecal segments. In the herbivorous animals, such as the guinea-pig and rabbit, in which, as Starling [6] noted, a large part of the process of digestion and absorption goes on in the proximal portion of the colon, the latter is adapted for this, being capacious, with

4. Jacobj, Carl: Pharmakologische Untersuchung über das Colchicumgift, Arch. f. exper. Path. u. Pharmakol. **27**:119 (April 10) 1890.

5. Elliott, T. R., and Barclay-Smith, E.: Antiperistalsis and Other Muscular Activities of the Colon, J. Physiol. **31**:272 (June 30) 1904.

6. Starling, E. H.: Principles of Human Physiology, ed. 4, Philadelphia, Lea & Febiger, 1926.

big absorbent flaps of mucous membrane projecting into its interior. In the guinea-pig, these form a valve between the cecum and the proximal half of the colon which can resist a pressure of several inches of water seeking exit to the colon, but which yields readily to fluid moving with the current of antiperistalsis.

In Elliott and Barclay-Smith's studies on the dog, they never saw antiperistalsis, although the cecum contracted often and with apparently great force, but it did this with complete independence of movements in the other portion of the colon. They consider the cecum in the dog nonfunctional and dwindling, and that the current that has produced it has disappeared. This, in general, is in agreement with Bayliss and Starling's [7] observations, who considered the motor activity of the dog's colon as peristaltic; similar studies by Zondek [8] and also by Lurje [9] on the cat, rat, guinea-pig and other mammals confirmed Elliott and Barclay-Smith's results. Templeton and Lawson,[10] in their studies on the movements of the large intestine of the dog, by a system of balloons, were unable to detect any contractions which they could classify definitely as antiperistaltic.

In 1909, Cannon [11] again carefully studied the movements of the colon and, in corroborating his former observations, attempted to explain the origin and mechanism of antiperistalsis. He regarded the presence of tonic rings of constriction as of significance in the initiation of both peristaltic and antiperistaltic contraction, in substantiation of findings described by Biedermann [12] in 1904. He designated these tonic waves, in the colon as well as in the small bowel, as a persistent shortened condition of the musculature and suggested that it was due to continued excitation. Cannon,[13] in 1911 and 1912, reported further work along this line and emphasized the importance of internal pressure in its influence on movements of the colon. With the presence of a tonic ring

7. Bayliss, W. M., and Starling, E. H.: The Movements and Innervation of the Small Intestine, J. Physiol. **24**:99 (May 11) 1899; The Movements and the Innervation of the Large Intestine, ibid. **26**:107 (Dec. 31) 1900.

8. Zondek, B.: Study of Peristalsis, Arch. f. Verdauungskr. **27**:18, 1920; abstr., J. A. M. A. **76**:346 (Jan. 29) 1921.

9. Lurje, H. S.: Untersuchungen über die motorische Funktion des Dickdarms: IV. Untersuchungen am überlebenden Dickdarm, Arch. f. d. ges. Physiol. **212**:64, 1926.

10. Templeton, R. D., and Lawson, H.: Studies in the Motor Activity of the Large Intestine: I. Normal Motility in the Dog, Recorded by the Tandem Balloon Method, Am. J. Physiol. **96**:667 (March) 1931.

11. Cannon, W. B.: Further Observations on the Myenteric Reflex, Am. J. Physiol. **23**:xxvi, 1908-1909.

12. Biedermann, W.: Studien zur vergleichenden Physiologie der peristaltischen Bewegungen, Arch. f. d. ges. Physiol. **102**:475 (May 21) 1904.

13. Cannon, W. B.: The Relation of Tonus to Antiperistalsis in the Colon, Am. J. Physiol. **29**:238 (Dec.) 1911.

of contraction, the internal pressure on adjacent parts of the intestinal wall is raised, the contraction regions nearby thus being distended and stimulated, with waves passing in each direction. However, he explains that as the contents of the colon are more viscous as they approach the median portion, so in the presence of a tonic ring, with fluid on one side and a viscous mass on the other, the effect would be different. On the side of the latter, the ring could not distend the wall and the wave would not pass distally, but proximally (antiperistalsis). The distal content could be moved by a contraction of the ring, and this is what Elliott and Barclay-Smith saw in the rat and other animals. If the contents were soft, the movements were likely to be antiperistaltic, but if the contents were dry and hard, peristalsis was the usual result, thus showing that the consistence of the feces was of significance in determining the type of movement present. The tonic ring of contraction was maintained after destruction of the spinal cord and, no doubt, the result of increased internal pressure. Balli [14] has enumerated seven definite situations in the colon which, in reality, are spastic areas, although he designated them as sphincters, and further stated that these are the points of origin of antiperistaltic and peristaltic waves. They are as follows: (1) in the ileocecal area; (2) between the cecum and the ascending colon; (3) in the cecocolic area in the proximal segment of the ascending colon; (4) in the transverse colon, at the juncture of its first and third portions; (5) at the splenic flexure; (6) at the juncture of the sigmoid and descending portions, and (7) between the sigmoid and the rectum. Other factors influence these waves, such as intestinal gases, and Henderson [15] has shown that the carbon dioxide content of the blood may be of importance to a certain extent in the activity of the bowel.

In 1918, Alvarez and Starkweather,[16] studying intestinal gradients of rhythmicity, irritability and metabolism, showed that these were present in the colon as well as in the small intestine. They suggested that the herbivora, with their rough, less easily digested, bulky foods and their thin-walled bowel, need a more even gradient than the carnivora. In the cat and the dog, the lower end of the gradient was often reversed, and this may save these animals from frequent calls to defecation. Accentuation of this reversal of gradient, they explain, may be present with some types of constipation.

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14. Balli, R.: The Sphincters of the Colon, Radiology **12**:484 (June) 1929.

15. Henderson, Yandell: A Method for the Direct Observation of Normal Peristalsis of the Stomach and Intestines, Proc. Soc. Exper. Biol. & Med. **6**:67, 1908-1909.

16. Alvarez, W. C., and Starkweather, Esther: The Metabolic Gradient Underlying Colonic Peristalsis, Am. J. Physiol. **47**:293 (Dec.) 1918.

Meltzer and Auer [17] watched the intestinal movements through the shaved abdominal wall of the rabbit and saw peristaltic waves, but did not mention antiperistalsis; likewise, Alvarez [18] stated that in this animal peristaltic waves seem to be very rare.

Thomas and Kuntz [19] observed reversed movements near the cecum in a dog, and Lenz,[20] using a celluloid abdominal window in a cat, definitely established the presence of antiperistaltic waves, regarding them as movements of retention. Likewise, Basler,[21] in 1909, saw churning movements in rats and cats. Groves, in 1909, injected a colored fluid into the rectum of a boy with a cecal fistula and saw this fluid come from the fistula in jets every four or five minutes. It was not in a continuous stream, so he was strongly inclined to the view that antiperistalsis was responsible for the backward movement of this fluid. Smith-Shand [22] saw large antiperistaltic waves in the proximal portion of the colon in a case of obstruction of the colon at the sigmoid flexure, and Schwarz [23] saw a similar type of movement in a patient with chronic constipation.

Further evidence of the presence of antiperistaltic waves in the proximal portion of the colon has been substantiated by experiments in which reversal of a segment of the cecum or ascending portion of the colon has been done. This type of work is similar to that done on the small bowel in which these waves no doubt take place. In 1907, Beer and Eggers [24] reversed 6 inches (15 cm.) of ascending colon and obtained results similar to those found after a similar operation has been done on the small bowel; namely, peristaltic waves descend from the ileum across the upper anastomosis and then along the reversed loop but stop at the distal anastomosis. Circular contractions follow each other in the reversed loop in the same direction as normal peristaltic waves. Likewise, as in the small intestine, the reversed segment of

17. Meltzer, S. J., and Auer, John: Peristaltic Movements of the Rabbit's Cecum and Their Inhibition with Demonstration, Proc. Soc. Exper. Biol. & Med. **4**:37, 1906-1907.

18. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, P. B. Hoeber, Inc., 1928.

19. Thomas, J. E., and Kuntz, Albert: A Study of Gastro-Intestinal Motility in Relation to the Enteric Nervous System, Am. J. Physiol. **76**:606 (May) 1926.

20. Lenz, E.: Observations à la fenêtre abdominale "colique" du chat: I. Mouvements intestinaux normaux et action péristaltogène des purgatifs anthraquinoniques, Arch. internat. de pharmacodyn. et de thérapie **28**:75, 1923-1924.

21. Basler, Adolf: Beiträge zur Kenntnis der Bewegungsvorgänge des Blinddarminhaltes, Arch. f. d. ges. Physiol. **128**:251 (May 28) 1909.

22. Smith-Shand, A. K.: Antiperistalsis in the Large Intestine, J. Roy. Nav. M. Serv. **4**:367, 1918.

23. Schwarz, Gottwald: Zur Physiologie und Pathologie der menschlichen Dickdarmbewegungen, München. med. Wchnschr. **58**:1624 (July 25) 1911.

24. Beer, Edwin, and Eggers, Carl: Are the Intestines Able to Propel Their Contents in an Anti-Peristaltic Direction? Ann. Surg. **46**:576, 1907.

colon contains foreign bodies, and dilatation at the upper union takes place where the opposed peristaltic waves meet. Fluid material passes through the loop readily. It is believed that antiperistalsis takes place here, propelling the content of the loop onward, yet the results are not convincing since adaptability of the bowel to new conditions may explain the entire situation. In 1923, Muennich [25] studied antiperistalsis on excluded intestinal segments. He found (contrary to Roith's [26] opinion that antiperistaltic waves cease from the middle transverse portion of the colon downward) that they seemed to be present in the entire organ. He demonstrated a backward flow in cases of ileosigmoidostomy, thus explaining the filling up of the colon back to the cecum and no doubt resulting in the untoward symptoms seen in cases of this nature. Albrecht [27] reported a similar case, and likewise concluded that antiperistalsis in the excluded segment was the explanation of the phenomenon. Blamoutier,[28] in 1925, using roentgenoscopic methods, saw antiperistaltic waves in all portions of the colon except the rectum, and even occasionally noted them in this segment of the large intestine. Cannon,[13] in 1911, stated that reverse movements are present, and that retrogression of feces from the rectum may take place by this movement. It commonly occurs after repression of desire for defecation. However, the rectum may often be full of feces, as Alvarez [18] and other clinicians have found during examinations of the pelves of women, so that retrogression is not always the rule.

The possibility that antiperistaltic movements can be the cause of vomiting has been disputed. Beer and Eggers [24] and Nothnagel [29] stated that vomiting of formed feces and of enemas introduced into a normal gastro-intestinal tract cannot be explained on any other basis. Alvarez quoted a number of authors who have observed the stomach in vomiting and rarely have they observed reversed movements. Alvarez suggested that a general reversal of the intestinal gradient may occur in which the colon takes only a small part.

Colored substances have been injected into the rectum and the subsequent course watched. Bond, in 1905, showed that particles of carmine can travel from the anus back to the cecum and even higher by

25. Muennich, G. E.: Unilateral Intestinal Exclusion, Surg., Gynec. & Obst. **36**:773 (June) 1923.

26. Roith, O.: Ueber die Peristaltik und Antiperistaltik des menschlichen Dickdarmes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:203, 1912.

27. Albrecht, Hans: Zur Frage der Antiperistaltik im Dickdarm bei schwerer Obstipation, München. med. Wchnschr. **59**:1592 (July 16) 1912.

28. Blamoutier, P.: Les mouvements antiperistaltiques du gros intestin, Paris méd. **55**:325 (April 4) 1925.

29. Nothnagel, C. W. H.: Beiträge zur Physiologie und Pathologie des Darmes, Berlin, A. Hirschwald, 1884.

"reverse currents." Grützner,[30] Nothnagel and Starling used similar methods, but their conclusions were against the presence of so-called reverse currents. However, their experiments were performed on dogs, and in these animals antiperistalsis probably does not occur, at least not to any considerable degree.

The introduction into the rectum of an enema, such as saline solutions, by means of the Murphy drip proctoclysis, is followed by transportation by antiperistalsis of the fluid to the proximal or absorbing portion of the large intestine, and explains the disappearance of large quantities of fluid introduced in this manner.

Roentgenographic studies on antiperistaltic movements in the colon of man have contributed much of value. Stierlin,[31] in 1910, and Stierlin and Fritzsche [32] saw reverse transport of feces in the colon of baboons but could detect no such activity in the large intestine of man. Kaestle,[33] in 1912, Serena,[34] in 1913, and Guarini,[35] in 1919, were of the same opinion, after making studies of a similar nature. Schwarz,[36] in 1911, found contractions occurring in an anal as well as an oral direction, but could not determine which were most pronounced. Hertz and Newton,[37] in 1913, by filling the colon with an average-sized opaque enema, saw the fluid run passively to the cecum but with a slight excess. Contractions were stimulated, and the fluid passed in both directions from contracting segmental rings. The latter were associated with a desire to defecate. In agreement with Walsham and Overend [38] and Isémein and Poinso,[39] they were still in doubt as to whether these waves were antiperistaltic.

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30. Grützner, P.: Ueber die Bewegungen des Darminhaltes, Arch. f. d. ges. Physiol. **71**:492 (May 4) 1898.

31. Stierlin, Eduard: Ein Beitrag zur radiographischen Untersuchung der Kolonperistaltik, Ztschr.f.klin.Med. **70**:370, 1910.

32. Stierlin, Eduard, and Fritzsche, E.: Verhandl. d. deutsch. Kong. f. inn. Med. **29**:183, 1912.

33. Kaestle: Die Bewegungsvorgänge des menschlichen Dünn und Dickdarmes während der Verdauung auf Grund röntgenographischer und röntgenkinematographischer Untersuchungen, München. med. Wchnschr. **59**:446 (Feb. 20) 1912.

34. Serena, M.: Studio dei piccoli movimenti del colon col seriografio, Atti d. Cong. ital. di radiol. med. **1**:161, 1913.

35. Guarini, C.: Osservazione di movimento colico, Radiol. med. **6**:99, 1919.

36. Schwarz, Gottwald: Zur genaueren Kenntnis der grossen Kolonbewegungen, München. med. Wchnschr. **58**:2060 (Sept. 26) 1911.

37. Hertz, A. F., and Newton, Alan: The Normal Movements of the Colon in Man, J. Physiol. **47**:57 (Oct. 17) 1913.

38. Walsham, Hugh, and Overend, Walker: On the Movements of the Colon, Arch. Radiol. & Electroth. **20**:260 (Dec.) 1915.

39. Isémein, Léon, and Poinso, Robert: Physiologie des côlons, Gaz. d. hôp. **97**:897 (July 5) 1924.

Lenz,[40] in 1919, noted a retrotransport of feces in the colon of man due to a strongly active contraction directed orally, but he did not consider this as identical to antiperistalsis. Case [41] stated that reversed waves are the prevailing type of movement in the proximal colon and that they may become exaggerated in the presence of obstruction lower, thus resulting in stasis in the proximal segment. He called attention to the fact that many writers have described gangrene of the cecum associated with obstruction in the pelvic or sigmoid portions of the colon, and explained the phenomenon as due to waves of antiperistalsis originating at a tonic contraction ring creating back pressure, resulting in distention of the cecum. Blamoutier,[28] in 1925, definitely saw this type of contraction ring from which waves of antiperistalsis seem to arise. He commented on the fact that the ileocecal valve would soon atrophy if it were not for the presence of reverse waves.

Movements other than antiperistalsis take place in the proximal colon. Cannon [42] stated that there are several of these, the first of which he called the serial sectioning movement. This consists of the separation of a small segment in the cecum by a constriction, followed by a second constriction which cuts off another segment just above the first, and with the disappearance of the first constriction, the separated segments unite. A third segmentation then takes place above the second and the changes again occur, thus sectioning the whole mass. Another movement consisting of broad constricting bands appearing and relaxing results in a gentle kneading of the contents. He also noted other movements in the ascending colon, such as strong constricting rings, forcing the contents into the transverse colon. Sometimes these started at the ileocecal valve, but more often they originated in the ascending portion, usually without visible stimulation. Elliott and Barclay-Smith found what they called "propulsive peristalsis" which was present throughout the colon in the animals they studied and which was responsible for the downward movements of the contents.

Holzknecht's [43] opinion was that the colon of man rests most of the time and is active only three or four times each day. He saw masses of feces pass through the colon for a considerable distance almost instantaneously and called them "mass movements."

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40. Lenz, Emil: Der retrograde Transport im Dickdarm des Menschen, sein Wesen, seine physiologische und klinische Bedeutung, Arch. f. Verdauungskr. **25**: 54 and 128, 1919.

41. Case, J. T.: Surgical Physiology and Pathology of the Colon from the X-Ray Standpoint, New York State J. Med. **21**:156 (May) 1921.

42. Cannon, W. B.: Peristalsis, Segmentation and the Myenteric Reflex, Am. J. Physiol. **30**:114 (April) 1912.

43. Holzknecht, G.: Die normale Peristaltik des Kolon, München. med. Wchnschr. **2**:2401 (Nov. 23) 1909; The Normal Peristalsis of the Colon, Arch. Roentgen Ray **14**:273 (Feb.) 1910.

These belong more properly to movements of the left half of the colon and will be considered later. Stierlin [31] found that the cecum possessed the least motor capacity of any portion of the colon. Schwarz, in his fluoroscopic work on the large intestine, found that the latter was never at rest but was continually moving and at times capable of very intensive, rapid contractions, leading to considerable displacement of its content toward the anus. The observations of Kaestle, Hertz and Newton, Case, Walsham and Overend, Hertz,[44] Lenz,[40] Lignac,[45] Guarini, Isémein and Poinso, and Blamoutier are of similar nature.

In summarizing the movements of the proximal portion of the colon, it may be stated that this segment is a mixing and absorbing one, and the movements here are not so pronounced or well defined as in the remainder of the large intestine, which is the propelling segment.

*Functions of the Haustra and Taeniae.*—At this point, it may be well to consider the functions of the haustra. Lineback [46] has made the most recent and most extensive studies on the subject. On the outer surface of the colon there are three lines of thickening of the longitudinal muscle layer called the taeniae, which are well defined in the adult. These are shorter than the colon; so they have the property of decreasing its length and thus causing the intervening parts of the intestinal wall to be drawn or puckered into folds called haustra. Kaestle [33] and Katsch [47] think these folds may be produced by the local constriction of circular fibers, but it is probably true that both factors operate to produce the condition. Lineback, corroborating Lowitz's [48] observations, showed that many small bundles of fibers pass from the longitudinal layers to the circular layers, so that the latter are somewhat thinned in the region of the taeniae. By roentgen studies he noted that the waves of contraction in the circular muscle which produce clefts in each of the three regions between the taeniae occur independently, and rarely do two clefts or zones of contraction occur exactly opposite each other on each side of the taeniae. The effect is usually limited to one region between the taeniae. This is due mainly to the fact that the circular fibers are not strong enough to draw down the taeniae into a

44. Hertz, A. F.: Constipation and Allied Disorders, London, Henry Frowde, 1909.

45. Lignac, Pierre: Les mouvements rétrogrades du colon et leur étude radiologique, Presse méd. **27**:52 (Jan. 30) 1919.

46. Lineback, P. E.: Studies on the Longitudinal Muscle of the Human Colon, with Special Reference to the Development of the Taeniae, Contrib. Embryol. **11**: 35, 1920.

47. Katsch, Gerhardt: Der menschliche Darm bei pharmakologischer Beeinflussung seiner Innervation, Fortschr. a. d. Geb. d. Röntgenstrahlen **21**:159, 1914.

48. Lowitz, G. A.: Recherches sur l'appareil musculaire du gros intestin chez l'homme et quelques mammifères, Thèse de Bordeaux, no. 41, 1896, p. 32.

cleft and the latter, therefore, act more or less as strong, fixed, longitudinal cables on which the former pull. Thaysen,[49] in 1916, by roentgen studies, found that the shape of the haustra could be altered by the finer contractures of the circular muscles within them. Courtade and Guyon,[50] studying both of these layers, concluded that the inferior mesenteric nerve principally controlled the circular muscle, and the sacral nerve the longitudinal muscle, which confirmed Biedermann's [51] work, suggesting separate nerve control of the two layers.

Kaestle studied the function of the haustra minutely in his fluoroscopic work on the colon of man, especially those in the proximal portion, and showed that here the food is thoroughly kneaded and mixed by their alternate broadening and narrowing. He also observed complete contraction of the haustra, either singly or simultaneously in groups, concluding that the occurrence of deep haustration was physiologic and emphasizing that it was not a spastic phenomenon. He also saw changes in positions of the haustra due to narrowing and widening of the colon over varying lengths, and in the distal part of the colon haustral processes were not so complicated although invaginations and bulgings were observed, as well as segmentation of spherical balls of feces. Hertz and Newton compared the haustral movements to segmentation of the small bowel, and Case, and Howell [52] found them almost constantly in action, mixing materials and aiding in propelling the contents onward. Rutherford [53] observed in a patient with a fistula of the cecum that a haustrum grasped a small, moist mass of feces, enveloped it, and then retained it until dry, when it was pushed back into the lumen of the bowel.

*Mechanism of Peristalsis in the Colon.*—The mechanism by which movements of the digestive tract, as well as those of other involuntary muscles, take place has been carefully worked out by a number of investigators, but with by no means conclusive results. It has been well established that rhythmic contraction is an inherent property of muscle and muscle-like tissue, which fundamentally is brought about by recurring cycles of chemical activity, and no doubt these are myogenic in origin, although they can be stimulated and coordinated by

49. Thaysen, T. E. H.: Ueber den Bau und die Entstehung der Haustra coli, Anat. Hefte **54**:321, 1916-1917.

50. Courtade, D., and Guyon, J. F.: Innervation motrice du gros intestin, Compt. rend. Soc. de biol. **49**:745, 1897.

51. Biedermann, W.: Zur Physiologie der glatten Muskeln, Arch. f. d. ges. Physiol. **45**:369, 1889.

52. Howell, W. H.: A Text-Book of Physiology, ed. 10, Philadelphia, W. B. Saunders Company, 1927.

53. Rutherford, A. H.: The Ileocecal Valve, New York, P. B. Hoeber, Inc., 1914.

nerves and nerve plexuses. In the bowel this is done especially by Auerbach's plexus which is attached to the longitudinal coat and communicates outside the bowel by the extrinsic nerves. Whether these movements downward are explainable according to Bayliss and Starling's [7] law of the intestine, to Keith's [54] theory of nodes or to Alvarez's gradient idea is not yet proved. The happenings in the gastro-intestinal tract are readily explained by the presence of gradients, and Alvarez conceived of a number of these as present, such as of pulling force, of tone, of rhythmicity and of irritability, although he considered the fundamental and underlying gradient metabolic, and gave logical and clearcut explanations.

There have been many explanations regarding the mechanism by which the movements of the colon take place. Bayliss and Starling,[7] in 1901, saw contractions in the dog pass from the ileum directly on over to the large intestine, and these were present also after complete enervation of extrinsic nerves. Alvarez, however, considers the ileocecal sphincter a barrier to most of the movements as well as to the contents of the ileum, although he saw a few waves pass on down into the colon in a rabbit. He presented evidence showing that by the folding of the muscle layers this leads approaching waves into a blind pocket where they are lost. This is in agreement with Luciani's [55] observation that peristalsis of the colon is usually not a continuation of that of the small bowel. Alvarez and Starkweather show that irritability in the cecum is low, probably due to the poor development of Auerbach's plexus here, which accounts for the fact that it acts so well as a reservoir and is little influenced by movements elsewhere in the digestive tract. Many cases of so-called cecal stasis have been attributed to defects in Auerbach's plexus, as well as to the position of the colon and to maldevelopments.

Bayliss and Starling considered inhibition to take place below the point of stimulation in the large as well as in the small bowel, and the same inhibitory effect to take place below a descending peristaltic wave. They found it difficult to demonstrate an ascending type of excitation in the colon, as compared to the small bowel, but they concluded that the movements are under the control of a local nerve mechanism, and peristaltic waves are due to a combination of ascending excitatory and descending inhibitory impulses. Their opinion was that these usually started in the local nerve plexuses due to the presence of a stimulating agent in the lumen of the bowel. Cannon [13] found a refractory period present during the period of shortening, similar to that found in the

54. Keith, Arthur: Cavendish Lecture on a New Theory of the Causation of Enterostasis, Lancet **2**:371 (Aug. 21) 1915.

55. Luciani, Lugi: Human Physiology, New York, The Macmillan Company, 1913, vol. 2.

stomach and small bowel. Elliott and Barclay-Smith, studying the mechanisms of antiperistaltic waves, presumed them to be immediate myogenic responses to distention and correlated them to the churning movements of the small bowel. Alvarez's gradient idea explains the phenomena of movements in the colon in a logical manner. The ileocecal sphincter normally has a gradient of irritability higher than that of the ileum, thus explaining backward reflection of waves over the ileum, the sphincter functioning as an effectual barrier. The muscle of the colon is more sluggish than that of the ileum, and segments of the tip of the cecum were less irritable than those from the base. In studying the movements of the cecum, he found the gradient to be upward from the base of the cecum, through to the remainder of the colon, thus explaining its reservoir function. He showed that normally the tone of the rectum and sigmoid is higher than that of the colon immediately above; this he noted to be helpful in keeping fecal matter from packing up against the sphincter, and this explains how sometimes feces are returned to the upper part of the colon when defecation is postponed. Defecation can be readily supposed to take place when the gradient above becomes so steep or that of the sigmoid and rectum so lowered that the fecal material moves downward. In a similar manner, interference or an abnormal gradient may explain constipation, postoperative ileus, vomiting, gastric dilatation and dyspepsia.

*Studies of Movements of the Colon with Various Types of Enemas.*—The introduction of the opaque enema along with roentgenoscopy or fluoroscopy, and the use of other types of enemas, have afforded an important means of studying the physiology of the colon. Cannon,[3] in 1902, made many observations, using roentgenographic methods, and thought that enemas in general stimulated antiperistalsis of the colon; the movements sometimes lasted over an hour, but usually they were not strong enough to force the contents through the ileocecal valve unless the enemas were very large. However, he once saw these waves in a normal subject, after using an extremely small enema, so came to no definite conclusions. In the cat a small enema of 25 cc. of the opaque mixture first lay in the descending colon; then reverse waves were soon set up and the material was forced back into the cecum, but nothing went through into the small intestine. With from 90 to 100 cc., it was often observed to pass through the ileocecal valve. Schwarz,[23] in 1911, found that considerable stimulation to contraction of the colon was obtained by use of various enemas, and his observations in human beings were similar to those of Drummond,[56] who noted that enemas rarely go beyond the cecum; in other words, the ileocecal valve was usually com-

56. Drummond, Hamilton: Observations on the Functions of the Colon, with Special Reference to the Movements of Enemata, Brit. M. J. **1**:240 (Jan. 31) 1914.

petent. Hertz [44] found that if more than 750 cc. of fluid was used in human beings, the colon contracted and expelled the contents, and he thought that hydrostatic pressure alone brought about passage of fluid to the cecum. Drummond tried this on cadavers and found that the fluid passed backward just as rapidly as in the living person.

Joltrain, Baufle and Coope [57] produced pressure of various kinds in the large bowel and noted the effects. They found that the normal colon can hold about 1,000 cc. of fluid, which they computed was under a pressure of from 16 to 20 cm. height of water and created no distress. With various diseases of the large intestine the capacity was much less and the pressure under which it was retained was much greater. When the pressure rose to around 30 cm. of water, with a volume of 3,000 cc. in the colon, the patients complained of pain and distress. Burt [58] determined the pressure required to rupture the bowel at various levels by the introduction of air. He found the rectum to support the greatest average pressure, with the sigmoid, ileum, esophagus, jejunum, transverse colon, cecum and stomach in order of their rupture. The greatest pressure supported was 11.59 pounds per square inch. In the rectum of a child, aged 11 years, and in adults, the average was around 8.36 pounds per square inch. The practical application of Burt's work lies in the emphasis of care in instrumentation in proctology, in administration of enemas and in the breaking up of impacted fecal masses. Friedenwald and Feldman,[59] in 1931, studied the detrimental effect of prolonged use of various enemas. Using tap water once daily for one hundred and fifty-five days, they saw a few hemorrhagic areas in two of three animals; with soap, only one of three had this appearance; with cotton seed oil, there were no changes, but with a solution of sodium bicarbonate, the typical clinical and pathologic picture of chronic ulcerative colitis was produced in each of the animals observed.

Betz found reflex contraction of the large intestine after the injection of a glycerin enema as high as the hepatic flexure, and Alvarez's view is that many times the effect may go much further. He voiced the experience of others in noting that patients occasionally become nauseated from ordinary injections of physiologic solution of sodium chloride and vomit when anything a little more irritating is introduced, such as soap, glycerin, turpentine or dextrose. This also gives founda-

57. Joltrain, E.; Baufle, P., and Coope, R.: Essai de mesure de la pression du gros intestin. Ses variations. Application a la clinique, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:211, 1919.

58. Burt, C. A. V.: Pneumatic Rupture of the Intestinal Canal with Experimental Data Showing the Mechanism of Perforation and the Pressure Required, Arch. Surg. **22**:875 (June) 1931.

59. Friedenwald, J., and Feldman, M.: Experimental Studies on the Effect of Prolonged Use of Colon Enemas upon the Bowels in Animals, Am. J. Surg. **11**: 23 (Jan.) 1931.

tion for the opinion that part of the nausea and distress, and even of the vomiting, following abdominal operations may be due to the use of the Murphy drip type of apparatus for rectal instillation of fluids, and, in fact, several authors have commented on this. Rolleston and Jex-Blake [60] noted that in a series of ninety-six patients with gastric disturbances who were fed by rectum, twenty-six vomited at some time or other, and Bine and Schmoll [61] advised against the use of enemas in the presence of fecal vomiting, because in this condition any fluids instilled in the rectum would be liable to be vomited. The explanation of the phenomenon, as Alvarez stated, is a reversal of the normal gradient, with waves traveling in the opposite direction, due to the stimulation of the lower end of the tract by the irritating enemas.

The movements of the colon were studied by the authors with a tandem set of three balloons in the isolated large intestine of the dog. In this type of preparation in which nearly normal conditions were maintained, the ileum was connected to the sigmoid as closely as was anatomically possible and the two ends of the colon were brought out as in cecostomy and sigmoidostomy, respectively. In this manner, the influence of anesthesia as well as operative trauma could be excluded. Kymographic tracings were made of the movements by the use of small balloons connected to a water manometer system. The position of the balloons as checked at postmortem examination was found to be in the cecum, at the splenic flexure and in the lower part of the sigmoid. By administration of various cathartics through the stomach, definite activity could be elicited in this isolated loop such as that accompanying defecation, vomiting or the gastrocolic reflex.

One of the most evident facts that impresses one in this study is the marked difference in activity between the cecum and the remainder of the colon. The cecum was constantly active and from these movements of mixing and churning it could easily derive its important function of absorption. Whether these contractions are antiperistaltic or peristaltic, or whether they are the result of local stimulation was difficult to determine, but at any rate they were definitely of different character than those of the distal portion of the colon. They seem to represent a higher degree of irritability than is found elsewhere in this organ. Normally the distal part of the colon was almost completely inactive, showing only small, almost imperceptible contractions which probably were the effect of respiration. However, when activity did take place the most frequent movements were systolic pulsations and not peristaltic waves. The latter type of contraction was rarely definitely identified.

60. Rolleston, H. D., and Jex-Blake, A. J.: On the Occurrence of Vomiting During Rectal Alimentation., Brit. M. J. **2**:68 (July 11) 1903.

61. Bine, René, and Schmoll, Emile: The Treatment of Gastric and Duodenal Ulcer, California State J. Med. **12**:361 (Sept.) 1914.

Many authors have found the colon never inactive but continually showing some degree of motility. These movements of the large intestine indicate a high degree of efficiency which has been developed, and show the adaptations of this organ to mechanical conditions which are present. The activity of the cecum promotes absorption and aids in retaining the fecal material until the consistence is such that it acquires form and is then pushed on though the transverse colon to the splenic flexure. From here it is transported by coarser movements and undergoes little change until it is expelled. Disturbances in this absorptive or expulsion function, such as retaining the feces in a liquid state throughout, or on the other hand, drying them too much, may account for some cases of diarrhea and of constipation, as many authors have suggested.

It is a common clinical observation in patients with diarrhea that after eating there are abdominal distress, cramps and the urge to evacuate the bowels, and also that the patient is definitely more comfortable between meals. There seems to be no doubt that there is a definite relationship between the ingestion of food and defecation in both normal human beings and animals. In the present series of experiments on the so-called gastrocolic reflex, the latter was definitely elicited in spite of the fact that there was lack of continuity in the intestinal tract between the stomach and colon, so that the possibility of an impulse running down the bowel by either neurogenic or myogenic means to stimulate the colon must be eliminated. In this connection, Alvarez quoted Short,[62] who noticed that the coils of the ileum were always active except during fasting, but when food was taken little gushes of succus entericus appeared at the ileocecal sphincter in from one and a half to four minutes. Likewise Cannon,[13] in 1911, showed that as food enters the cecum a fresh series of waves is initiated there. Lyman [63] further demonstrated what he called a "receptive relaxation" of the colon when food entered it from the ileum, similar to that of the cardia as its contents pass through the esophagus. He also noticed that as soon as the small bowel had finished emptying itself through the ileocecal sphincter and had again become quiet, the large intestine became active. His explanation is that there was reciprocal innervation of the two portions of the bowel. Surmont, Dubus and Tiberghien [64] sectioned the ileum near the cecum and could produce movements in

62. Short, A. R.: Observations on the Ileo-Caecal Valve in Man, Brit. M. J. **2**:164 (Aug. 9) 1919.

63. Lyman, Henry: The Receptive Relaxation of the Colon, Am. J. Physiol. **32**:61 (May) 1913.

64. Surmont, H.; Dubus, A., and Tiberghien, P.: Contractions coliques consécutives a des excitations prépyloriques et duodénales, Compt. rend. Soc. de biol. **71**:641, 1911.

the colon by irritation of the stomach. Likewise, Alvarez, in 1924, cut the bowel across and found that although no waves crossed this opening, yet simultaneous movements took place in many parts of the intestine, and he was of the opinion that nerves in the mesentery served to carry these impulses. The mechanism of the gastrocolic reflex he explained on a similar basis; this seems the most reasonable in accounting for the presence of this type of activity in the colon in this series of experiments.

### MOVEMENTS OF THE DISTAL, OR LEFT, HALF OF THE COLON

The movements of the left half of the colon are antiperistalsis, which most investigators agree takes place, at times especially, in connection with a similar type of activity in the right half of the colon, and coordinated peristalsis, which drives the content onward, similar to that of the small bowel. Several other types of movements in the colon have been reported. The best understood of these are the strong contractures which evacuate the bowel. Elliott and Barclay-Smith noted that these were slow, powerful constrictions of the tube commencing at a point a considerable distance up the colon and running downward to empty the contents, an action common to all animals and a fundamental reaction to stimulation of the sacral nerves. Most of our knowledge of the movements of the colon has been gained by means of roentgenograms, either an opaque meal or an opaque enema being used.

Cannon,[3] in 1902, found that as the content from the proximal colon was pressed gradually onward toward the transverse and descending portion of the colon, a deep constriction appeared near the advancing end and almost separated a globular mass from the main body of food. The contents progressed farther along the colon, and new tonic constrictions appeared which separated the contents into globular masses. As these increased in number, they got farther from the cecum, although they were present chiefly in the descending colon. Raiser [65] recorded similar observations in the colon of the rabbit, in which deep circular constrictions separated the scybalous masses. Thus, as Cannon [13] brought out, these rings of constriction, moving slowly from the cecum, pushed the hardening contents before them. It is obviously an advantage to have them pushed through in divisions rather than in a uniformly cylindric mass, and while this is going on, some absorption takes place within the confines of these rings. Kaestle explained the facility with which the contents of the colon were moved forward as due to an advancing column of gas which opened up the lumen of the bowel before it.

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65. Raiser, K. P. T.: Beiträge zur Kenntnis der Darmbewegungen (Giessen). Worms am Rhein, A. K. Boeninger, 1895.

Schwarz [23] added that increased abdominal pressure was of considerable significance in moving the fecal material along the colon, and that in constipation and in stenotic lesions of the bowel he could see the segmentation contractions somewhat accentuated, and even hypermotile, depending on the degree of occlusion of the lumen of the bowel. Serena, in 1913, made similar observations, and Bergmann [66] and Schwarz [23] noted that contractions were markedly activated under the influence of distending enemas. Walsham and Overend stated that these movements are due to true peristaltic waves, with a rate of from one to two a minute, and that they are abolished by nicotine or curare and probably originate from nodal tissue. Walsham and Overend described smaller rhythmic contractions with waves coming at the rate of about twelve each minute, which they claimed had no directive power but exhibited periodic augmentation and were either purely myogenic or myoneurogenic. These were practically identical to those observed by Isémein and Poinso. Hurst,[67] in 1922, found that the tonus and movements of the colon depend largely on the bulk of its contents, and these varied continuously with the amount of gas and feces present. He also observed that the descending and pelvic portions of the colon were usually empty and consequently in a state of tonic contraction with more or less obliteration of its lumen, whereas the opposite condition was present on the right side. Here the content was fluid or semifluid, the tonus was less and the lumen greater, so that he considered it normal to find a large splashy cecum when the portion of colon felt on the left side gave the impression of a solid cord. From his roentgenologic observations on human subjects, he noted that the colon was quiet most of the time and only changed materially after hours in which a meal was taken.

Hickey [68] found the movements of the colon by the barium sulphate enema so slow and so infrequent that opportunities to observe them were rare, and in most cases, whether the colon is filled by a barium meal or by a barium enema, the examiner can report only the size, shape and relation of the component parts of the large intestine. However, by overdistending the organ with large enemas of opaque material he saw peristalsis begin in the transverse colon and pass along to the splenic flexure, forcing the content onward and distending the upper portion of the descending colon. The content may be interrupted temporarily here but it soon passes on, emptying the lower portion of the descending colon and starting up peristaltic waves in the sigmoid which may result in

66. Bergmann, quoted by Schwarz.[36]

67. Hurst, A. F.: Sins and Sorrows of the Colon, Brit. M. J. **1**:941 (June 17) 1922.

68. Hickey, P. M.: Peristalsis of the Colon, Am. J. Roentgenol. **9**:260 (April) 1922.

evacuation. About this time peristalsis starts in the cecum, emptying it rapidly and passing onward to the transverse colon where the procedure again takes place. Flint [69] holds an opinion similar to that of Hickey in that he found the colon quiet most of the time except after meals, and Murray [70] stated that normal peristalsis does not take place until the colon is full. Macleod [71] regards the descending colon as a tube for the transferring of masses from the transverse colon; he claims it is never distended. Rokitansky, in 1842, stated that this portion of the colon is normally empty. This fits in well with the study of Gleize-Rambal,[72] who observed that there is a line of demarcation between the transverse and descending portions of the colon which makes the distal colon well suited for strong muscular efforts to evacuate it. The descending portion is smaller and rounder and maintains its shape with greater ease than the transverse portion which is large, thin-walled and transparent. Microscopically, the muscularis of the descending portion is thick, and that of the proximal portion is poor in longitudinal fibers. He also found the cellular structure denser and thicker on the transverse portion with correspondingly greater amounts of mucus in this region. His observations were made on cadavers, at laparotomy and roentgenographically. Similarly, Kirkes [73] found that the muscular fibers of the colon become stronger as they progress distally, and are strongest in the rectum where greatest tension is exerted. Schellberg [74] considered the attachment of the colon at the hepatic and splenic flexures as important in the performance of their movements, which, he stated, are deliberate and seldom take place. Mills [75] described three movements of the colon expressed in relation to the colonic rugae, in which Forsell [76]

69. Flint, Ethelbert: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) **15**:54, 1922.

70. Murray, D. H., in discussion on Beach, W. M.: The Subnormal Function, J. A. M. A. **71**:1453 (Nov. 2) 1918.

71. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, ed. 5, St. Louis, C. V. Mosby Company, 1926.

72. Gleize-Rambal, L.: Sur l'individualité anatomique du côlon descendant, Compt. rend. Soc. de biol. **99**:2015, 1928; L'individualité structurale du côlon descendant, ibid. **100**:368, 1929; Note sur la disposition du gros intestin de l'embryon humain du 3e mois, ibid. **100**:715, 1929.

73. Kirkes, W. S.: Handbook of Physiology, ed. 16, New York, William Wood & Company, 1900.

74. Schellberg, O. B: Observations on the Physiology of the Human Colon, Internat. J. Med. & Surg. **41**:40 (Jan.) 1928.

75. (*a*) Mills, A. E.: Some Effects of Disturbance of Physiology of Movements of Gastro-Intestinal Tube, M. J. Australia **1**:127 (Feb. 7) 1925. (*b*) Mills, R. W.: Studies of the Colon: I. Roentgen-ray Evidence of Colonic Secondary Changes, Am. J. Roentgenol. **11**:487 (June) 1924.

76. Forsell, quoted by Mills.[75 b]

agreed. These, he stated, are: (1) the lateral or nonhaustral canalicular, (2) the general polydirectional haustral and (3) the longitudinal haustral compression movements.

Lenz [20] studied the movements of the colon of the cat through a celluloid abdominal window; Katsch and Borchers [77] have described the technic of this method in detail and saw two types of propulsive movements, annular and tubular, which were entirely distinct from those of defecation. Zondek,[78] in 1921, made a similar study of various animals and observed peristaltic movements occurring with considerable regularity in the dog about every thirty seconds; these were markedly stimulated by the taking of food. He also described haustral segmentation by a similar means in the colon of rabbits, and antiperistalsis as the usual finding in the proximal portion of the large intestine in the cat, rat, guinea-pig and other mammals. Plant and Miller,[79] using balloons in the colons of unanesthetized dogs, observed waves similar to those obtained by Templeton and Lawson. The latter investigators used a tandem set of six balloons in the dog's colon, three of which were inserted through a cecostomy opening and three through the rectum, and obtained some excellent records of the character of the movements of the large intestine. With this preparation simultaneous tracings were made of the entire colon. In the proximal portion, activity was distinctly periodic with contractions superimposed on changes in tonus, whereas in the distal portion changes in tonus were less pronounced but otherwise similar. The point at which the change took place was at the splenic flexure. They also found that the entire colon could act as a unit, but that the activity was subject to sudden alterations in the formation of waves going in either direction. In general, their results confirm those of other investigators.

*Mass Movements.*—One of the most interesting and frequently disputed movements of the colon is the so-called mass movement, it was described by Hertz [80] in 1907 and 1908, Hertz, Cook and Schlesinger [81]

77. Katsch, Gerhardt, and Borchers, Eduard: Beiträge zum Studium der Darmbewegungen. I. Das experimentelle Bauchfenster, Ztschr. f. exper. Path. u. Therap. **12**:225 (Jan. 8) 1913.

78. Zondek, B.: Ueber Dickdarmperistaltik, Beobachtungen am experimentellen Bauchfenster, Arch. f. Verdauungskr. **27**:18, 1920; abstr., J. A. M. A. **76**:346, (Jan. 29) 1932.

79. Plant, O. H., and Miller, G. H.: Effects of Carminative Volatile Oils on the Muscular Activity of the Stomach and Colon, J. Pharmacol. & Exper. Therap. **27**:149 (March) 1926.

80. Hertz, A. F.: The Pathology and Treatment of Chronic Constipation, Proc. Roy. Soc. Med. (Sect. Med.) **1**:119, 1908.

81. Hertz, A. F.; Cook, F., and Schlesinger, E. G.: The Action of Saline Purgatives, Guy's Hosp. Rep. **63**:297, 1909.

in 1909, Holzknecht in 1909, Barclay [82] in 1912 and Kaestle in 1912, and later by many others. Previous to the paper by Holzknecht in 1909, there seems to be no detailed statement concerning the mechanics of the propulsion of the fecal content over considerable areas, and credit should be given him for recognizing and describing these movements in detail. In brief, this movement is as follows: It is the principal normal propulsive movement of the colon taking place three or four times a day, serving to move the contents of the bowel from the antiperistaltic influence of the proximal portion of the colon through to the distal portion. The mechanism, as Holzknecht explains, may possibly be a powerful peristaltic wave, but more likely is associated with a tonic contraction of the circular coat of the part of the colon through which the wave passes. The haustral markings disappear and fecal matter seems to run together in a sausage-like bolus, which has smooth edges and is rounded at the ends. The mass at once begins to move at about twice the rate of peristaltic waves in the stomach, and the rate and distance of this movement are variable, sometimes transporting the fecal content from the cecum to the pelvic colon or rectosigmoid without stopping. When it comes to rest, haustral indentations reappear. Alvarez observed these mass movements often secondary to a rush wave in the small bowel and frequently resulting in a call to defecation. According to Case, they are most often seen before or during defecation. These movements are accompanied by a gurgling sound, due, Kaestle stated, to the accumulation of gases in advance of the moving mass, and expanding the colon ahead, thus facilitating movements over long distances. Diarrheal cramps, Case stated, are often accompanied by mass movements, and Alvarez saw these contractions in patients with a tendency to diarrhea. Kaestle noted these movements in a woman; the entire colon took part, contracting down to the size of a cord, but it was so marked and long continued, as well as accompanied by such severe spasmodic pain, that he concluded it was due to a disorder of innervation of the colon. Hertz,[44] in 1909, and also Welch,[83] in 1925, noted perceptible progress through the colon after meals, but otherwise this was very slow. Barclay,[84] in 1911, 1912 and 1913, studied these movements carefully and blamed defects in mechanism of this type of activity as resulting in stagnation in the rectum and other parts of the colon, and being one of the causes of constipation. In a further study in

82. Barclay, A. E.: Note on the Movements of the Large Intestine, Arch. Roentgen Ray **16**:422 (April) 1912.

83. Welch, P. B.: What Constitutes Constipation: Some Observations on Colon, J. Iowa M. Soc. **15**:18 (Jan.) 1925.

84. Barclay, A. E.: Radiological Studies of the Large Intestine, Brit. J. Surg. **2**:638, 1914-1915. Barclay [82].

1909 and again in 1913, Hertz,[85] and also Betz, in 1912, corroborated Holzknecht's view and added that the chief stimulus to this movement is entry of food into the stomach, and designated it as the gastrocolic reflex. Holzknecht, incidentally, noted the mass contraction after feeding a second bismuth meal. Hertz [44] further observed that normally the ileocecal sphincter held back the content in the terminal ileum for a considerable time, relaxing principally during meals, at which time the greater part of the content entered the cecum. Peristalsis in the lower part of the ileum became more activated at meal time. Hertz and Newton, in 1913, saw the phenomenon in a patient with partial intestinal obstruction due to carcinoma of the rectosigmoid juncture, and noted that the contents of the colon passed from one end to the other in a second or two, with no signs of either peristalsis or antiperistalsis.

Isémein and Poinso explained the mechanism of the gastrocolic reflex as consisting either of stimulation of the colon by a hormone from the gastric mucosa or of stimulation of the circular muscles of the small intestine down from the stomach and extending to the large bowel. Likewise, Betz, in 1912, considered the stomach and rectum as the principal reflex routes for stimuli to the intestine. Alvarez regarded the gastrocolic reflex as involving the mesenteric nerves.

In 1916, Walsham and Overend reported observations on sporadic mass movements following chiefly either the entrance of food into the empty stomach or evacuation of the bowel, and again in 1922, Hurst corroborated these observations, stating further that after the absorption of water from the contents of the right half of the colon the fecal matter is moved from the cecum to the pelvic colon, where it remains until mass movement carries it farther. They found that during the day the greater part of the cecal, ascending and pelvic portions of the colon are more or less full and the remaining part is empty. In a careful study, Welch and Plant,[86] using balloons placed in the stomach and colons of dogs through fistulas, and in the colons of human subjects, obtained tracings. Their observations showed that the normal muscular activity of the colon is very irregular and great variations in tonus and contractions occur, with the colon never in the state of complete inactivity which Holzknecht found. After feeding the dogs, they obtained a definite increase in tonus of the colon in from half a minute to several minutes, lasting from ten to twenty or up to sixty minutes. Sometimes this reaction would be repeated several times, but more often there was no second effect. By feeding through a fistula in the stomach, such results were not obtained. They therefore claimed that to call this

85. Hertz, A. F.: The Ileo-Caecal Sphincter, J. Physiol. **47**:54 (Oct. 17) 1913.

86. Welch, P. B., and Plant, O. H.: A Graphic Study of the Muscular Activity of the Colon, with Special Reference to Its Response to Feeding, Am. J. M. Sc. **172**:261 (Aug.) 1926.

reaction a "gastrocolic reflex" was a misnomer and that it is really a "feeding reflex" or "appetite reflex," similar to that of gastric secretion, depending not on distention of the stomach with food but more on psychic stimulation. They further substantiated this opinion by obtaining a typical result with merely the entrance of the attendant who usually fed the dog. They also demonstrated that with an empty bowel the effect was much less or was even absent, as contrasted to that obtained when the bowel was full. Schellberg, in 1928, considered the presence of gas as important in mass movements, and also that chemical activity of the fecal content on the mucosa played a considerable part in this and other types of movements of the colon. Draper and Johnson [87] disagree with former opinions of mass movements and stated that propulsion of the contents of the colon takes place by slow imperceptible segmentation contractions and probably not by so-called "mass movements" which they were never able to see. Hines, Lueth and Ivy,[88] in 1929, put balloons into the rectums and sigmoids of human subjects, through a proctoscope. They found two definite types of curves, one a slow, slight rhythmic elevation with a tonus rhythm and the other steep contractions. Among twenty-one normal students they obtained a steep contraction in five only after meals, and this was concomitant with an urge to defecation. They felt this was probably the gastrocolic reflex of other investigators. Such urge was not present if the subjects were constipated, and steep waves could not be obtained at any time with similar technic. They concluded, therefore, that the threshold for sensation in cases of constipation is raised. They also concluded that the latter type of movement is an involuntary aid to defecation. Movements similar to the mass contraction of Holzknecht were obtained by Ganter and Stattmüller.[89] Using a balloon in the colonic stoma of a patient with chronic ulcerative colitis, they obtained high contractions in groups similar to those obtained by Hines, Leuth and Ivy. Peiper,[90] by putting a double balloon in the distal colon of children, found that usually there was no activity, although if diarrhea was present there was a pendular type of movement.

*Defecation.*—Cannon,[3] in 1902, observed the process of defecation by roentgenographic means and described it as a slow, sweeping move-

87. Draper, J. W., and Johnson, R. K.: The Pathogenic Colon: Recent Studies, Am. J. Surg. **4**:1 (Jan.) 1928.

88. Hines, L. E.; Lueth, H. C., and Ivy, A. C.: Motility of the Rectum in Normal and Constipated Subjects, Arch. Int. Med. **44**:147 (July) 1929.

89. Ganter, G., and Stattmüller, K.: Studien am menschlichen Darm: III. Ueber die normalen Dickdarmbewegungen des Menschen und ihre Beeinflussung durch Pharmaka, Ztschr. f. d. ges. exper. Med. **42**:143, 1924.

90. Peiper, Albrecht: Bewegungen des Magen-Darmkanals im Saüglingsalter. 4. Der Dickdarm, Jahrb. f. Kinderh. **120**:312, 1928.

ment in which the bowel swung around so that the ascending colon lay in the position of the distal half of the transverse portion, and the latter took the position of the descending part. At the same time tonic contractions disappeared and were replaced by strong, broad contractions of the circular muscle, tapering the contents off on each side into two cones. As the intestine swung around, more material was forced into the rectum by constriction, dividing the lumen, which passed slowly downward aided by the abdominal musculature. Usually some material was left behind in the cecum. Hertz [44] described this act as consisting of contractions of the diaphragmatic and abdominal muscles which resulted in a considerable increase in pressure in the abdomen since the glottis was kept closed, aiding in forcing more feces into the rectum. Through the stimulation thus produced in the rectum, involuntary peristalsis starting well back in the colon was initiated. Included in this chain of reflexes was inhibition of the internal sphincter. His impression was that the entire colon took part in the act, but that only the bowel distal to the splenic flexure was evacuated, and in some cases even the rectum was not completely emptied. The content of the right part of the colon moved over to the descending colon to take the place of that which was evacuated. Schwarz's [28] observations were of a similar nature, except that he saw fecal masses go through almost the entire length of the colon and this movement was associated with contractions of that organ. By the introduction of stimulating enemas he demonstrated a similar process, and could by this method obtain evagination and invagination of the haustra. He further demonstrated roentgenologically that prior to, and during, defecation there regularly occurred coarse movements of the large intestine. These occurred typically as cramps and were often associated with diarrhea. Schwarz [23] attributed propagation of intestinal contents to the fine and coarse movements of the large intestine and also to the increased intra-abdominal pressure. In this connection it may be noted that Jonas,[91] in 1912, found in his studies on achylia gastrica that diarrhea was associated with a hypermotility of the entire gastro-intestinal tract and not necessarily of the large bowel alone. Also, he noted that if the propulsion of the contents was abnormally fast in the small intestine, a normal stool could still result, providing there was a delay in the passage through the distal portion of the colon.

There probably is no distinct desire to empty the bowels until feces have actually reached the rectum and produce distention there, as Howell has pointed out, and as Hertz and Newton, in 1913, were able to see roentgenographically. The feces are retained by tonic contraction of the

91. Jonas, Siegfried: Ueber das Verhältnis zwischen Stuhlbild und Darmmotilität und die wechselnden Stuhlbilder der Hyperacidität und der Achylie, Arch. f. Verdauungskr. **18**:769, 1912.

internal sphincter until defecation begins, then the sphincter relaxes and masses are forced through the anal canal by the combined efforts of the rectal and abdominal muscles. In other words, it is normally both a voluntary and an involuntary action. The minimal pressure within the rectum found by Hertz [44] to initiate a call to defecation was between 3 and 4 mm. of mercury, and the pressure within the rectum may become from four to eight times that much during the act as a result of the increased intra-abdominal pressure. The latter then caused more material to enter and to distend the rectum, and resulted in still stronger contractions of abdominal and rectal muscles as well as a corresponding relaxation of the internal sphincters. Severe pain may be produced by using extreme distention in the colon, as Fröhlich and Meyer [92] have shown. They attributed this either to spasm of the circular musculature or to irritation of the peritoneal coat. Alvarez noted a tendency sometimes in man to empty the rectum completely by a process of prolapse and eversion of the mucous membrane, and Starling stated that the last section of the rectum is emptied at the close of defecation by forcible contractions of the levator ani and other perineal muscles, contractions which serve to restore the everted mucous membrane. Luciani considered peristaltic activity of the sigmoid and rectum as most essential in the act of defecation, although inhibition of tone of the internal sphincter, contractions of the levator ani and abdominal compression by contractions of the diaphragm and abdominal musculature along with closure of the glottis are important factors.

A spurious desire to move the bowels may be aroused by pressure from external sources on the walls of the rectum, such as from a large calculus of the bladder, prostatic tumor or fetal head in the pelvis. The same effect may be noticed from internal hemorrhoids, tumor of the rectum or an inflammatory disease present in that region.

Defecation may be restrained by several muscles or combinations of muscles, such as the internal sphincter, the external sphincter, the levator ani and the voluntary muscles about the perineum, as Frankl-Hochwart and Fröhlich [93] pointed out.

There are other factors which influence or take part in the act of defecation, namely, centers in the brain and spinal cord. Hatcher and Weiss,[94] in 1923, applied small doses (0.016 mg.) of picrotoxin to an area in the floor of the fourth ventricle close to the vomiting center and produced diarrhea almost immediately, and Luciani, in 1913, found

92. Fröhlich, A., and Meyer, H. H.: Die sensible Innervation von Darm und Harnblase, Wien. klin. Wchnschr. **25**:29 (Jan. 4) 1912.

93. Frankl-Hochwart, L., and Fröhlich, Alfred: Ueber Tonus und Innervation der Sphinkteren des Anus, Arch. f. d. ges. Physiol. **81**:420 (Aug. 11) 1900.

94. Hatcher, R. A., and Weiss, Soma: Studies on Vomiting, J. Pharmacol. & Exper. Therap. **22**:139 (Oct.) 1923.

areas in the brain where stimulation affected the tonus of the sphincters. However, it is probable, as Alvarez stated, that the most important centers for the sphincters are in the third and fourth sacral segments of the cord. This was substantiated by Goltz,[95] and also by Goltz and Ewald's [96] observations that immediately after destruction of the lumbar and sacral cord in dogs, the anus was relaxed and gaping. Occasionally there was diarrhea, but this gradually cleared. In time defecation became normal and there was no atrophy of the sphincter, showing that the rectum and sphincters act by virtue of their own intrinsic mechanism, a faculty which Alvarez attributed to the high autonomy of the rectum.

When there is nothing to start the chain of reflexes which brings about defecation, such as loss of sensation in the rectum, it is then that the most severe disturbances are produced. Merzbacher,[97] in 1902, demonstrated this by cutting the sensory roots of the three sacral nerves of the dog. The animals were not aware of anything in the rectum because of the anesthesia produced. The feces became dried out, no attempt was made by the animal to defecate, and it was only when a considerable amount of material collected in the rectum that it was pushed out passively. This is likewise true in human subjects, as noted by Bálint and Benedict,[98] in 1905 and 1906, who studied six cases of lesions of the conus terminalis and found that the patients were generally constipated in spite of relaxation of the anal ring and anesthesia of the mucosa of the rectum. However, they could control the bowel movements fairly well. These observers made no roentgenographic observations of the colon. McIntosh,[99] in 1929, confirmed this in observing a child, aged 6 years, with a lesion of the spinal cord in the lumbosacral area. He found marked stasis of the colon; it took a barium meal twelve days to reach the rectum and longer to be expelled. It took ten days for it to pass from the splenic flexure down so that most of the retardation was in the left portion of the colon. The tonus of the large bowel was apparently good, the haustra appeared normal, and there was no localized atony or dilatation. McIntosh agreed with other observers in that it seemed to him that the trouble was chiefly

95. Goltz, F.: Ueber die Functionen des Landenmarks des Hundes, Arch. f. d. ges. Physiol. **8**:460, 1874.

96. Goltz, F., and Ewald, J. R.: Der Hund mit verkürzten Rückenmark, Arch. f. d. ges. Physiol. **63**:362, 1896.

97. Merzbacher, L.: Die Folgen der Durchschneidung der sensibeln Würzeln im unteren Lumbalmarke, im Sacralmarke und in der Cauda equina des Hundes, Arch. f. d. ges. Physiol. **92**:585 (Nov. 5) 1902.

98. Bálint, R., and Benedict, H.: Ueber Erkrankungen des Conus terminalis und der Cauda equina, Deutsche Ztschr. f. Nervenh. **30**:1 (Dec. 20) 1905.

99. McIntosh, Harriet C.: Roentgenologic Study of the Colon in a Child with a Spinal Cord Lesion, Am. J. Roentgenol. **22**:247 (Sept.) 1929.

sensory impairment of the rectum and that there was no excitant to initiate mass movements. Also, there was no sudden entry of a large amount of material into the rectum as there is when mass contractions take place. Peculiarly enough, it is the experience of neurologists that there is no definite relationship between the level of the situation of a tumor of the spinal cord and the degree of disturbance of sphincter function.

The fact that most people perform the act of defecation in the morning soon after breakfast is generally ascribed to several factors. During the night the contents of the colon are gradually moved from the proximal to the pelvic and descending portions, and after being comparatively quiet the large bowel is stimulated to activity by the muscular exercise in moving about and by reflex contractions from putting food into the empty stomach. The chain of reflexes thus set up results in a call to defecation.

*Valves of the Rectum.*—The function of the valves of the rectum has been studied by various investigators. Bodenhamer,[100] however, denies their existence as definite valves, claiming them to be merely semilunar ridges of mucous membrane. Pennington[101] described them in detail and stated that they have definite functions, according to his experimental studies on both living and dead subjects. He found that the valves function to prevent feces from crowding down on the anus, that they equalize the pressure of the feces that accumulate in the rectum from time to time and that they facilitate defecation by giving a spiral motion to the content of the bowel. In support of his views, he cited the fact that man is the only animal possessing them and he is the only animal that defecates regularly. Irritants and foreign bodies cause them to become erect and present as a sort of ledge across the bowel, and in some cases they are directed upward, forming distinct cups or pockets, as demonstrated in plaster casts taken of them. In certain subjects they are enlarged, sometimes so much that they may interfere with normal defecation.

*Other Movements of the Colon.*—A fifth variety of movement takes place in the colon, which is described ordinarily as a pendulum or large swinging type of motion, and has been observed chiefly during roentgenologic studies. These movements seem to be concerned especially with the aid of absorption and take place in the transverse colon. This portion of the colon assumes a totally different position, first being in a high and in a few minutes in a lower part of the abdomen.

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100. Bodenhamer, W.: Are There Veritable Valves in the Rectum? New York M. J. **71**:1026 (June 30) 1900.

101. Pennington, J. R.: New Points in the Anatomy, Histology, and Pathology of the Rectum and Colon, Chicago M. Rec. **19**:392, 1900.

This motion was described by Walsham and Overend, in 1916, by Rieder,[102] and by Currie and Henderson,[103] in 1926, who also noted gentle swaying movements in direct observations on the colon of the guinea-pig, which they thought were produced mainly by the longitudinal muscles. In addition to the type of movement studied by the aid of the roentgen rays, by abdominal windows and by direct observation, valuable contributions have been made by the observation of strips of bowel excised from the large intestine.

Alvarez commented on the sluggishness of the colon and exhibited many tracings to show the contractions of excised bits of its musculature, which reveal a very slow rate with pronounced tonus waves. From five different segments of the cecum there was little difference, the beats possessing little rhythmicity, as compared with that of the small bowel. Kolda,[104] in 1926, made similar observations on the large intestine of the cat and obtained six contractions, at the rate of six in five minutes, and these were of a similar nature to Alvarez's results. From the studies of Alvarez and Starkweather, there appears to be a downward metabolic gradient (determined by the catalase content) from the tip to the base of the cecum of rabbits and guinea-pigs. From the base the gradient is upward to the colon. They bring out a physiologic reason for this difference in that the cecum is a food reservoir which, in order to retain its contents, contracts seldom and is not influenced by happenings in the other parts of the gastro-intestinal tract. Cannon,[13] in 1911, showed that mechanical extension was the most efficient stimulus for exciting activity in the colon, just as it is for other types of smooth muscle such as that of the small bowel, ureter and bladder. Magnus,[105] in 1904, seems to have been first to record the longitudinal movements of short length strips of bowel, which has been called the Magnus method. Currie and Henderson used strips from the first part of the ascending colon of the guinea-pig and found small, rhythmic movements with a rate of about thirty-eight each minute, and at times larger contractions which they thought were the result of summation of the smaller ones. In the transverse colon, the strips beat rather irregularly with long, slow tonus waves, and in the sigmoid portions they obtained high tonus waves, but these were less frequent than those of the transverse segment.

102. Rieder, H.: Die physiologische Dickdarmbewegung beim Mensche, Fortschr. a. d. Geb. d. Röntgenstrahlen **18**:85, 1912.

103. Currie, G. C., and Henderson, V. E.: A Study of the Movements of the Large Intestine of the Guinea Pig, Am. J. Physiol. **78**:287 (Oct.) 1926.

104. Kolda, J.: Contribution a l'étude des mouvements de l'intestin isolé, Compt. rend. Soc. de biol. **95**:210, 1926.

105. Magnus, R.: Versuche am überlebenden Dünndarm von Saügethieren: II. Die Beziehungen des Darmnervensystems zur automatischen Darmbewegung, Arch. f. d. ges. Physiol. **102**: 349 (April 9) 1904.

Gross,[106] Flint,[68] Keith [107] and others noted the effect of a diet deficient in vitamins on the movements of the strips of colon of rats. Ordinarily, they beat with a rhythm of from two to three contractions each minute, but after deprivation of vitamin B, contractions were not elicited, and the result of this in vivo, they showed, was definite stasis in the intestinal tract. The latter was evidenced by dilatation of the ascending colon, by the filling of the descending colon with feces and by the presence of an increased number of ileocecal glands.

*Reflexes Involving the Colonic Movements.*—Many factors operate to aid in unifying and rendering the functions of the large intestine purposeful, and disturbance of or interference with any of these factors may lead to abnormal or ectopic movements. Just as with many other portions of the body, the colon is subject to reflexes, and although not many of these can be readily explained, yet a few have been studied thoroughly. Probably the most important of these is the gastrocolic or feeding reflex which has been described. Inflammatory lesions in the ileocecal region, such as appendicitis, may produce all grades of back pressure [18] up to the vomiting of large amounts of fluids and likewise intestinal injury, such as cutting and handling of the bowel, will delay the emptying time of the stomach.[11] This no doubt is a protective mechanism for the purpose of holding back food until the bowel becomes healed. Many investigators have shown that distention of the colon delays emptying of the stomach. White [108] produced intense irritation of the cecum of cats with mustard and olive oil, and also with croton oil, and obtained definite delay in the emptying of the stomach and even in vomiting. However, with a moderate or even a marked degree of irritation there was usually no effect. Smith and Miller [109] obtained increases in tonus as well as in peristaltic activity of the stomach and pylorus by irritation of the cecum or appendix with croton oil. Pearcy and Van Liere [110] distended the colons of dogs and found that during vigorous hunger contractions of the stomach the contractions ceased and complete inhibition took place. If the distention was continued, it

106. Gross, Louis: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) **15**:71, 1922.

107. Keith, Arthur: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) **15**:60, 1922.

108. White, F. W.: The Effect of Disease of the Lower Bowel on the Rate of Emptying the Stomach, Med. & Surg. **2**:618 (June-July) 1918.

109. Smith, F. M., and Miller, G. H.: The Reflex Influence of the Colon, Appendix and Gallbladder on the Stomach, Arch. Int. Med. **46**:988 (Dec.) 1930.

110. Pearcy, J. F., and Van Liere, E. J.: Reflexes from the Colon, Tr. Am. Gastro-Enterol. A., 1925, p. 135.

caused nausea, salivation and vomiting. Smith, Paul and Fowler [111] noted increases in activity of the stomach and especially of the pylorus when they injected air into the large intestine or massaged the cecum of patients with an irritable colon. They thus showed the presence of a definite reflex involving the colon and stomach. King [112] has shown that stimulation of the colon caused inhibition of the motor, secretory and absorptive functions of the small bowel. Pearcy and Van Liere also obtained cardiovascular respiratory reflexes from distention of the colon consisting of what appeared to be auricular extrasystoles and auricular flutter. Blood pressure also rose from 30 to 60 mm. of mercury and in some cases in man, from 20 to 25 mm. of mercury, remaining elevated as long as nine hours, and the subjects complained of flushed skin and free perspiration. In dogs they obtained an increased volume of the kidney and increased tonicity of the bladder.

More recently, Monroe and Emery,[113] after determining normal values, studied the emptying time of the stomach following irritation of the colon by turpentine, and their results indicated that the emptying time of the stomach was not especially influenced by irritation of the colon. However, there was no involvement of the peritoneum in their experiments, so it is possible that the difference in results of other investigators may have been due to this.

In a different type of experiments, in which the conditions were reversed, Surmont, Dubus and Tiberghien [64] applied stimuli to the prepyloric and duodenal regions of dogs and cats and noted the effect on the colon. In some cases no reaction whatever could be elicited on the large intestine, but in many of them contraction waves were recorded in the colon within one minute of the time of stimulation in the upper part of the intestinal tract. This, they explained, was due to a reflex and not to a peristaltic wave passing downward, because there was not enough time for this to take place. They thought it might be related to the gastrocolic reflex. Lyman, in 1913, in confirming Cannon's [11] view that the proximal part of the colon becomes quiet and relaxed as food nears the ileocecal valve, observed cats anesthetized with ethyl carbamate and then injected a mixture of starch and paste into the ileum near the valve. He noted that the colon a moment before was in tonic contraction, but as the material passed through the valve, the large intestine became motionless and relaxed, and as soon as the process was finished waves reappeared in the colon. He concluded that the mecha-

111. Smith, F. M.; Paul, W. D., and Fowler, W. M.: Mechanism of Epigastric Distress Associated with an Irritable Colon and Chronic Appendicitis, Arch. Int. Med. **47**:316 (Feb.) 1931.

112. King, C. E.: Studies on Intestinal Inhibitory Reflexes, Am. J. Physiol. **70**:183 (Sept.) 1924.

113. Monroe, R. T., and Emery, E. S., Jr.: The Effect of Irritation of the Colon on the Emptying Time of the Stomach, Am. J. M. Sc. **177**:389 (March) 1929.

nism was a local one because he could obtain it in the absence of nervous connections to the spinal cord, and that it was an example of reciprocal innervation of opposed muscles.

Drury, Florey and Florey,[114] in 1929, exteriorized a small segment of colon and demonstrated that when the dog was frightened and when local stimulation was applied this patch would turn pale, even when it was denervated, but it would not necessarily do so during mass movements. Even with movements in the portion, pallor was not observed. They do not explain the nature of the phenomena. White increased the tonus of the colon and, in this way, stimulated peristalsis by vigorous massage of the contents of the large intestine under the fluoroscopic screen. Incidentally, he was unable to move fecal matter by such massage. The value of exercise in the correction of constipation no doubt can be explained on the basis of the massaging action of the abdominal musculature on the intestinal tract, as noted by Soper.[115] The effect of exercise on the behavior of the colon has been reviewed in detail and studied extensively in some researches of their own by DeYoung, Rice and Steinhaus.[116] By inserting single balloons into a cecostomy opening in the colon of the dog, with the animal on a treadmill, they obtained rises in the motility and tonus of this organ. This increased activity was not coexistent with the period of exercise but started from one to three minutes later and receded in a few minutes, regardless of the duration of the exercise. They attempted to trace the origin and nature of this rise from exercise by sectioning the colon near the ileocecal valve in some instances, and in others near the anus. With the balloon between the two "cuts," no "exercise" response could be elicited, but above and below the two cuts, typical results were obtained. From this they deducted that there is a second parasympathetic inflow to the colon, probably vagal, coming in at the proximal end of the large intestine, and movements are stimulated by an unusual outflow of impulses during exercise. (The sympathetic nerves were intact in these experiments.) DeYoung, Rice and Steinhaus consider these rises in tonus and motility with exercise as similar in nature to the "mass movements" seen in man. Other factors which stimulate movements of the colon are the presence of formed fecal material in the rectosigmoid, gradual intermittent dilatation of the anal canal, the presence of food in the stomach and the act of defecation.

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114. Drury, A. N.; Florey, H., and Florey, M. E.: The Vascular Reactions of the Colonic Mucosa of the Dog to Fright, J. Physiol. **68**:173 (Oct. 23) 1929.

115. Soper, H. W.: Studies of the Colon: II. The Restoration of Colonic Function, Am. J. Roentgenol. **11**:503 (June) 1924.

116. DeYoung, V. R.; Rice, H. A., and Steinhaus, A. H.: Studies in the Physiology of Exercise: VII. The Modification of Colonic Motility Induced by Exercise and Some Indications for a Nervous Mechanism, Am. J. Physiol. **99**:52 (Dec.) 1931.

*Motor Tests of Function.*—At present there are no known tests by which the estimation of the function of the colon may be determined with any degree of accuracy. It is true that by roentgenoscopic and other means the time required to empty the contents of the colon has been observed repeatedly, and some idea of the normal function of the large intestine can be obtained by these methods; yet individual variations are so great and so many factors, both extrinsic and intrinsic, exert their influence that these methods do not always seem to be reliable. Hertz,[44] in his observations, felt that the time required for a meal to be evacuated from the gastro-intestinal tract was about from thirty-three to forty-eight hours. He also found that the meal should reach the splenic flexure in about twenty-four hours, and this, in general, is the opinion of most roentgenologists. Kretschmer [117] believed the type of food itself to be a potent factor in the rate of passage through the intestinal tract; in general, coarse food progressed farther. The difference, he thought, was mostly in the small intestine and upper portion of the colon. Likewise, Burnett [118] stated that a badly proportioned dietary regimen was responsible for many disturbances in intestinal function, and the literature is replete with suggestions of this type. Elliott and Barclay-Smith, Schwarz, Carter,[119] Burnett and others have shown that there is a mixing of colonic contents, mostly in the right colon,[18] so that some of the fecal material may stay in the bowel as long as from three to five days, whereas some is voided the same day it is taken. This has been determined especially by the use of various colored beads, and Alvarez has shown that it may often be longer than this before a meal completely traverses the intestinal tract. By giving different colored small glass beads on three successive days, he found that most of his normal subjects passed only 75 per cent of the beads in about four days and after this it often was weeks before all were passed. After catharsis, the rate of passage was greatly increased and, following that, stool was not passed for a day or two, again emphasizing Alvarez's contention that after thorough defecation bowel movement should not be expected for a time because the gastro-intestinal tract is empty, rather than because of any astringent or constipating action by the drug. Naturally, the rates of emptying of the colon vary considerably; subjects with fast rates usually have soft, frothy and voluminous stools, possibly due to faulty digestion and absorption, and it may be that those with slower rates with well formed small stools show better digestion.

117. Kretschmer, Julian: Röntgenologischer Nachweis diätetischer Beeinflussung der Darmperistaltik, München. med. Wchnschr. **59**:2334 (Oct. 22) 1912.

118. Burnett, F. L.: Faulty Food Factors and Atonic Constipation, J. A. M. A. **83**:996 (Sept. 27) 1924.

119. Carter, L. J.: Fluoroscopic Study of the Large Bowel by the Opaque Enema: Analysis of Eight Hundred Examinations, J. Roentgenol. **2**:355, 1919; Further Report on the Study of the Colon by the Opaque Enema: Summary of One Thousand Examinations, Canad. M. A. J. **10**: 1112 (Dec.) 1920.

*Function of the Appendices Epiploicae.*—One of the characteristic findings by which the large intestine may be distinguished from the small intestine is the presence of the appendices epiploicae. They occur as small pouches of peritoneum in two rows, their line of origin being quite close to the anterior and posterior inferior longitudinal muscle bands, and extend from the cecum to the rectosigmoid juncture. No definite evidence of their true function is available, although many speculations have been made. W. J. Mayo [120] thought that they were capable of a wiping motion similar to the swaying movement of the small bowel, which aided in the defensive forces of the abdomen. Robinson [121] was of the opinion that they were concerned with movements of fluids in the colon, thus aiding absorption, but Harrigan [122] denied this, stating that their structure was simple and that they presented no evidence of a specialized function. It is Rankin's [123] belief that there is no doubt as to their being a part of the defensive mechanism, whether they move or not, because they so often are found sealed to a pathologic process, such as gangrenous appendicitis or diverticulitis. That these epiploic tags may get into mischief is evident from a series of observations by Hunt,[124] who described torsion of them with serious results.

### ABSORPTIVE AND EXCRETORY FUNCTIONS OF THE COLON

Although it is true that disintegration, digestion and absorption of various foods take place in different parts of the intestine, according to the nature of the aliment, yet there is divergence of opinion regarding the types of material and the mechanism by which absorption takes place in the colon. The anatomy of the colon has been widely studied with reference to its physiology. Starling, in 1926, pointed out that great differences exist in the structure of the colon in different animals, differences which depend not on the zoologic position of the animal but on the nature of its food. The colon of the carnivora is short and narrow with little if any cecum, and it has a relatively unimportant function to discharge in digestion and absorption. Proteins of meat are practically entirely absorbed by the time food reaches the ileocecal valve and the same applies to fats, so that only a small amount of these

120. Mayo, W. J.: The Principles Underlying the Surgery of the Stomach and Associated Viscera, Am. J. M. Sc. **133**:1 (Jan.) 1907.

121. Robinson, B. F.: The Transverse Colon and Its Meso-Colon in 140 Autopsies, M. Rev. **32**:348, 1895.

122. Harrigan, A. H.: Torsion and Inflammation of the Appendices Epiploicae, Ann. Surg. **66**:467 (Oct.) 1917.

123. Rankin, F. W.: Surgery of the Colon, New York, D. Appleton and Company, 1926.

124. Hunt, V. C.: Torsion of the Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

absorbs. The chief function of the colon of carnivora is that of excretion. The colon of the herbivora is well developed, with sacculated walls, and the cecum is very large. This is necessary because their nutritious matter is enclosed in cells surrounded by cellulose walls, and these must be disintegrated so that absorption can take place, which is accomplished either by bacteria or by ferments in the vegetable cells themselves. In the horse, it seems there is a digestive fluid from the cecum which acts on foodstuffs, either in vitro or in vivo. In the cecum, under the action of many bacteria, cellulose is dissolved and cells are opened up to allow the contents to escape.

The colon of man is a compromise between the herbivorous and the carnivorous type. Draper [125] claimed that, with reference to the colon, human beings are dogs at birth because of the poorly developed right half of the colon; he further stated that the left half of the colon is of extreme age, of constant and important function and of fixed morphology, compared to the right half. He looks on the persistence of the right segment of the colon of man as the dominance of the experimental lengthening by the herbivora, and considers it ill adapted to man's needs. In support of this he studied the gross form of a number of normal colons and found many variations in size, position and appearance of the right side of the large bowel, as contrasted with the absence of variation on the left side. Even racially there are differences in the length of the colon, as Miloslavich [126] has shown, which depend on changes in environment, food, mode of living and climatic and social conditions. As far back as 1835, Schultz,[127] and in 1849, Brückner,[128] commented on the storage capacity of the cecum and its possible function in digestion, and Keith,[129] W. J. Mayo and others have brought out the fact that the large intestine really begins near the splenic flexure, the right portion, especially the cecum, being more nearly like a second stomach. The right half of the colon simulates that portion of the small bowel with which it derives a common origin. Draper [125] claimed that absorption of water is the earliest known function of the right half of the colon. He also pointed out that the stomach and colon have a common function, storage and churning. In the stomach this serves to blend the water with the

125. Draper, J. W.: Developmental Reconstruction of the Colon: Animal Researches and Clinical Report of Twenty-Nine Human Cases, Ann. Surg. **67**:567 (May) 1918.

126. Miloslavich, E. L.: Racial Studies on the Large Intestine, Am. J. Phys. Anthrop. **8**:11, 1925.

127. Schultz, C. H.: Observations and Experiments upon the Functions of the Cecum, Edinburgh M. & S. J. **44**:408, 1835; London M. & S. J. **8**:427, 1836.

128. Brückner, Carl: Die Function des menschlichen Dickdarms mit Hinblick auf die der Wirbelthiere, Rostock, Adler's Erben, 1849.

129. Keith, Arthur: The Functional Nature of the Caecum and Appendix, Brit. M. J. **2**:1599 (Dec. 7) 1912.

ingesta and in the colon to remove it. Neither stomach nor colon aids materially in digestion and each can be dispensed with. Many observers have emphasized the water-absorbing function of the colon, stating that this takes place in the cecum between the ileocecal apparatus and the cecocolic sphincter, a physiologic muscular contracture near the hepatic flexure, further aided by the high attachment of the splenic angle so that fluids all tend to gravitate toward the right portion. If fluids went beyond this point, they would interfere with the storage function of the colon. W. J. Mayo summarized this by saying, "Man eats with his jejunum and ileum, and drinks with his cecum. He prepares his food with organs originating from the foregut and absorbs his nutrition from those derived from the midgut." In the small bowel, water is absorbed in large quantities but its loss is made good by diffusion or secretion of fluid in the intestine, since contents of the bowel at the ileocecal valve are quite as fluid as at the pylorus. In the colon, absorption of water is not compensated by a secretion, according to Howell. Hay [130] stated that absorption in the colon is slower than in the small bowel because of the very nature of the mucosa of the two portions, and also because of the mucus secreted in the large intestine which tends to inhibit absorption.

Regarding absorption of other substances, such as drugs, there is more question. Goldschmidt and Dayton,[131] and Goldschmidt and Binger,[132] using various salts, made extensive studies on the mechanism of absorption from the colon. Using dogs, anesthetized with ether or paraldehyde, they ligated the lower part of the ileum, placed a tube in the cecum and washed through to the anus. They found that distilled water was readily absorbed and that it did not injure the mucosa. They also noted that the colon did not have a one-sided permeability, because sodium chloride passed in or out of the colon, depending on the usual

130. Hay, M.: The Action of Saline Cathartics, J. Anat. & Physiol. **16**:243, 391 and 568, 1881-1882; **17**:62, 222 and 405, 1883; On the Use of Concentrated Solutions of Saline Cathartics in Dropsy, Lancet **1**:678 (April 21) 1883.

131. Goldschmidt, Samuel, and Dayton, A. B.: Studies in the Mechanism of Absorption from the Intestine: I. The Colon; A Contribution to the One-Sided Permeability of the Intestinal Wall to Chlorides, Am. J. Physiol. **48**:419 (May) 1919; II. The Colon; On the Passage of Fluid in Two Directions Through the Intestinal Wall, ibid. **48**:433 (May) 1919; III. The Colon; The Osmotic Pressure Equilibrium Between the Intestinal Contents and the Blood, ibid. **48**:440 (May) 1919; IV. The Colon; The Behavior of Sodium and Magnesium Sulphate Solutions, ibid. **48**:450 (May) 1919; V. The Colon; The Effect of Sodium Sulphate upon the Absorption of Sodium Chloride when the Salts are Introduced Simultaneously into the Intestine, ibid. **48**:459 (May) 1919.

132. Goldschmidt, Samuel and Binger, Carl: Studies in the Mechanism of Absorption from the Intestine: VI. The Colon; The Influence of Calcium Salts upon the Absorption of Sodium Chloride in the Intestine, Am. J. Physiol. **48**:473 (May) 1919.

law of osmosis and the level of sodium chloride in the blood. This differed somewhat from Diena's [133] point of view, who maintained that the quantity of such substances passing into the intestines is not related to the osmotic pressure of the liquid introduced. Goldschmidt and Dayton and Goldschmidt and Binger also found that the colon behaves toward a solution of sodium sulphate like a semipermeable membrane, but with magnesium sulphate there was almost no absorption into the blood stream, and the failure of absorption of this substance they regard as of significance in catharsis.

The question of absorption of dextrose from the colon has been dealt with extensively by McNealy and Willems.[134] They reviewed the literature carefully, and their experimental work added valuable knowledge to this subject. With fasting dogs under hypnosis by barbital, they isolated the colon by ligatures at the ileocecum and rectum, and likewise a segment of the lower part of the ileum, about 50 per cent longer, to give about the same absorbing surfaces. They found marked constancy in the absorbing action of the colon, but much variation in that of the ileum; this was checked by determination of blood sugar, taken not from the peripheral blood as it was by former investigators, but from the vessels draining the loop of bowel in which the dextrose had been placed. They found no rise in blood sugar in the blood taken from the loop of colon, but a marked rise in that taken from the ileum. With tap water, they found they could recover 78.6 per cent from the loop of ileum and 57.3 per cent from the loop of colon in an hour, and with physiologic solution of sodium chloride, 62.6 and 52 per cent, respectively, was recovered. McNealy and Willems' conclusions were that there was no appreciable absorption of 5 per cent dextrose from the colon, whereas there was considerable absorption from the ileum. Tap water and physiologic solution of sodium chloride were absorbed rapidly by both ileum and colon. The fate of a dextrose enema, according to them, is as follows: It may stay in situ indefinitely; it may be expelled; its character may be changed by bacterial or other action, absorption may take place, or it may pass into the small bowel. The latter is most likely, according to them, and the success of this type of enema is due to such a process, with consequent absorption in the ileum. In some further studies the same investigators found that the presence of 0.45 per cent sodium chloride in a 2.5 per cent solution of dextrose (a physiologic solution of sodium chloride) favored absorption of the dextrose to a certain degree. With the use of sodium bicarbonate and

133. Diena, G.: Studio sperimentale sull' assorbimento da parte dell' intestino, Arch. per le sc. med. **35**:62, 1911.

134. McNealy, R. W., and Willems, J. D.: The Absorption of Glucose from the Colon: A Preliminary Study of the Glucose Enema, Surg., Gynec. & Obst. **49**:794 (Dec.) 1929.

alcohol in a similar manner, they noted no influence on absorption of dextrose. There seems to be no doubt that fluids introduced by rectum are carried as far as the cecum. Whether this is by a reversal of peristalsis or by more mechanical pressure is debatable. Starling, in a study of a patient with a cecal fistula, calculated that 500 cc. of water passes the ileocecal valve in twenty-four hours, and about 400 cc. of this is absorbed, so he feels that the colon of man is of little significance as an organ of absorption.

A number of drugs have been studied from the standpoint of their absorption when given rectally. Hatcher and Wilbert,[135] Menninger and Heim,[136] Lesne, Hoskins,[137] Muirhead, and Barbour and Rappaport found epinephrine to be absorbed from the colon and to give the usual physiologic effect. However, Menninger and Heim found that giving the drug this way is unreliable, producing little if any effect in about half of the cases, but that whatever effect there is persists longer, hence it should be of advantage when long effect and repeated doses are required, as in Addison's disease. Levy gave digitalis rectally and found it taken into venous circulation chiefly by way of the mesenteric and portal systems. By a similar method, he gave sodium iodide, and by roentgenographic methods found it to be absorbed from the lower portion of the sigmoid; with bromides, a similar result occurred. It is commonly known that ether and other anesthetic agents are readily absorbable by rectum and produce narcosis.

Urine, without doubt, can be absorbed from the colon, and in birds and certain lower mammals this is probably at times a normal condition, because of the presence of the cloaca which acts as a common receptacle for ejection of both urine and feces. Baird, Scott and Spencer[138] showed that the entire output of urine cannot be drained into the upper part of the intestinal tract of a dog, as its absorption gives toxic symptoms that cause death in from seven to twelve days. Likewise, Cecil and Cummings,[139] after studying a case in which implantation of the ureters was made low in the colon, felt that prolonged absorption of these products occasionally produced a picture resembling chronic nephritis. However, at present, surgeons do not hesitate to

135. Hatcher, R. A., and Wilbert, M. I.: Pharmacology of Useful Drugs, Chicago, American Medical Association, 1915.

136. Menninger, W. C., and Heim, H. S.: The Rectal Administration of Epinephrin, Am. J. M. Sc. **172**:425 (Sept.) 1926.

137. Hoskins, R. G.: The Sthenic Effect of Epinephrin on Intestine, Am. J. Physiol. **29**:363 (Jan.) 1912.

138. Baird, J. S.; Scott, R. L., and Spencer, R. D.: Studies on the Transplantation of the Ureters into the Intestines, Surg., Gynec. & Obst. **24**:482 (April) 1917.

139. Cecil, A. B., and Cummings, R. S.: The Remote Effects of Absorption of Urine from the Colon: A Case of Traumatic Unilateral Uretero-Intestinal Anastomosis, J. Urol. **2**:469 (Dec.) 1918.

implant ureters into the colon, and they regard any dire results from absorption as unlikely.

Absorption of organic substances in the colon takes place to a much less marked degree than that of inorganic substances and is of considerable significance from the standpoint of the value of nutritional enemas as well as in the mechanism of digestion and absorption.

In spite of all the experiments made during the last few years, authors do not agree regarding digestion and absorption of nutritive matter by the colon. It occurs, of course, to a much larger extent in the ileum, as Reid [140] has shown, but studies on the large intestine are not so conclusive. Maestrini made colonic stomas at different levels in the colon of the rabbit and found that the total nitrogen occurred in largest amount in the first portion of the colon and diminished toward the middle of the transverse portion, and from that point to the rectum remained more or less constant. The maximal amount of soluble nitrogen was found in the ascending colon, and fats showed considerable diminution as far as the transverse colon, so that Maestrini claimed that in the rabbit nitrogenous compounds and fats at least are absorbed in the proximal portion of the colon. Reach [141] found absorption of gelatin was much greater from the large intestine when physiologic solution of sodium chloride was added, and Bernheim [142] commented on the apparent value of the nutritive enema by citing cases in which nourishment was given exclusively for as long as ten months by rectum. Eberhard [143] stated that 300 cc. of milk and two eggs could be absorbed by rectum in from one to two hours, and Mutch and Ryffel [144] found that 88 per cent of the nitrogen of peptonized milk could be utilized when given by rectum. The latter authors advised against the procedure, stating that toxic materials could be produced and absorbed in this manner, and recommended that only dextrose or saline solutions be given this way. Scheel [145] noted that milk and eggs irritated the rectum and were not absorbed, so came to conclusions similar to those of Mutch and Ryffel. Begtrup [146] tried meat and milk

140. Reid, E. W.: On Intestinal Absorption; Especially on the Absorption of Serum, Peptone, and Glucose, Phil. Tr., London, s.B **192**:211, 1900.

141. Reach, Felix: Ueber Resorption von Kohlehydraten von der Schleimhaut des Rectums, Arch. f. exper. Path. u. Pharmakol. **47**:231 (March 11) 1902.

142. Bernheim, Albert: Movements of Intestines, J. A. M. A. **36**:429 (Feb. 16) 1901.

143. Eberhard, H. M.: Nutrient Feeding per Rectum by the Drop Method, Am. J. Gastro-Enterol. **2**:5, 1912.

144. Mutch, N., and Ryffel, J. H.: The Metabolic Utility of Rectal Feeding, Brit. M. J. **1**:111 (Jan. 18) 1913.

145. Scheel, V., and Begtrup, E.: Nutrient Enemas, Ugesk. f. læger **77**:520 (April 1) 1915; abstr., J. A. M. A. **64**:1804 (May 22) 1915.

146. Begtrup, E.: Feeding by Way of the Rectum, Arch. f. Verdauungskr. **21**: 400 (Nov.) 1915; abstr., J. A. M.A. **66**:1062 (April 1) 1916.

amino-acids, along with sugar solutions, and stated there was a definite increase in elimination of nitrogen, so that no doubt some nitrogen was absorbed. In general, Cornwall [147] obtained similar results and recommended nutrient enemas of amino-acids with dextrose and other fluids to maintain nitrogen balance in cases in which food cannot be given by mouth.

Carnot and Bondouy [148] studied the content of the colon of a man through a cecostomy opening and found that carbohydrates pass rapidly into the cecum in which, for the most part, they are absorbed. The presence of starch in the cecum was noted from three to six hours after ingestion, and this also was soon absorbed. Egg albumin was found at the cecum in the form of albumin and albumose, but this gradually disappeared and albumin, albumose or peptone was not seen in the stool, indicating that some absorption took place.

In this connection, Howell showed that the splitting of the protein molecule is completed by the process of putrefaction, and the list of end-products is long: peptones, proteoses, ammonia and amino-acids; also indol, skatol, phenol, phenylpropionic acid, phenylacetic acid, fatty acids, carbon dioxide, hydrogen sulphide and marsh gas. Phenol, indol and skatol, he stated, are absorbed and excreted in the urine. However, from Carnot's and Bondouy's [148] study on the absorption of fats in the colon, they could come to no definite conclusions. They found neither biliary pigment nor bile salts at the cecum, although urobilin was present. Áldor [149] found that fats were slower to absorb when given by rectum than either carbohydrates or albumins. However, it seems that the main difficulty in dealing with nutrient enemas, according to Goodman,[150] is that a nitrogen balance cannot be maintained by their use alone, due to inability of the colon to absorb or to render absorbable nitrogen-containing compounds in the enemas. From Howell's observation it seems that considerable digestion may take place in the colon, as dogs with from 80 to 83 per cent of the small bowel removed seemed to get along quite well unless excess roughage or fat was given in their diet. Starling, however, stated that little if any absorption of egg albumin or caseinogen solution takes place by rectum. In his experiments, a small amount disappeared in a considerable time, and he considered this due to bacterial action. He concluded that feeding by

147. Cornwall, E. E.: A Plan of Rectal Feeding, J. A. M. A. **70**:1451 (May 18) 1918.

148. Carnot, P., and Bondouy, H.: État de la digestion au niveau du caecum, Compt. rend. Soc. de biol. **81**:487, 1918; État de la digestion au niveau du coecum, Arch. d. mal. de l'app. digestif **10**:123, 1919.

149. Áldor, Louis: Untersuchungen über die Verdauungs- und Aufsaugungsfähigkeit des Dickdarms, Zentralbl. f. inn. Med. **19**:161 (Feb. 19) 1898.

150. Goodman, E. H.: Diseases of the Digestive Tract and Allied Organs, the Liver, Pancreas, and Peritoneum, Progrès méd. **4**:17, 1915.

nutrient enemas is of no value and should be limited to saline solutions, water and dextrose.

*Excretion.*—That the physiology of the colon includes more than that of absorption and expulsion is evident from the numerous studies which have been made on its function as an excretory organ. Voit,[151] as far back as 1860, noted that in fasting dogs the amount of fecal material often exceeded the amount of food eaten, and since then many authors have noted that the excretion products of the intestinal mucosa take part in the formation of the fecal material. Peola [152] stated that in many instances the greatest quantity of feces is not made up of alimentary products, but of those of excretion from the intestine, and especially from the large bowel, although Voit stated that most of this excretion is confined to the small intestine. Voit further contended that almost all of the nitrogen content of the feces comes from intestinal secretions. Starling regarded the colon of carnivora chiefly as an excretory organ, since it played an important part in the elimination of calcium, magnesium, iron and phosphates, and he also mentioned that ulceration found in the large bowel following poisoning by mercury may be due to excretion of this drug by this route.

In his work on dogs, Draper [153] found that the right portion was relatively inactive as compared with the left portion in the excretion of various drugs and toxins. He noted that in poisoning by pilocarpine or diphtheria the mucosa of the proximal portion of the colon was bright scarlet, whereas that of the left portion remained normal. In 1929, Underhill, Peterman and Steel,[154] studying the fate of aluminum intravenously injected, found widespread elimination of the metal through the stomach and the small and large bowel. Bargen, Osterberg and Mann,[155] using dogs with colons isolated as previously described, except opening only at the cecal portion, studied the excretion of some of the heavy metals. They found that arsenic in the form of neoarsphenamine or meta-amino-para-oxyphenyl-arsenic acid, and mercury, mercurochrome and metaphen were excreted not at all or very little through

151. Voit, Fritz: Beiträge zur Frage der Secretion und Resorption im Dünndarm, Ztschr. f. Biol. **29**:325, 1892.

152. Peola, Flora: Sulla funzione emuntoria dell' intestino crasso, Gazz. d. osp. **46**:1181, 1925.

153. Draper, J. W.: Studies in Intestinal Obstruction, with a Report of Feeding Heterologous Jejunal and Ileac Cells to a Human Being, J. A. M. A. **63**:1079 (Sept. 26) 1914.

154. Underhill, F. P.; Peterman, F. I., and Steel, S. L.: Studies in the Metabolism of Aluminum: IV. The Fate of Intravenously Injected Aluminum, Am. J. Physiol. **90**:52 (Sept.) 1929.

155. Bargen, J. A.; Osterberg, A. E., and Mann., F. C.: Absorption and Excretion of Arsenic, Bismuth and Mercury: Experimental Work on the Colon, Am. J. Physiol. **89**:640 (Aug.) 1929.

the colon. Bismuth, they noted, whether given by mouth or intramuscularly, was eliminated through the large intestine. Peola commented on the serious inflammation of the intestinal mucosa and especially of the colon in uremia, and stated that toxic materials are probably eliminated by this route. He quoted a number of observers whose experiments show that under pathologic conditions, such as that in which the kidneys are impaired, urea, salts and medicinal substances may pass through the intestines. Renon and Ricket [156] found that sugar could be eliminated in the intestine in diabetes, so much so as to cause diarrhea at times. No doubt this may account for some of the attacks of diarrhea experienced by diabetic patients. Peola, in acute experiments, using isolated loops of colon, injected methylene blue (methylthionine chloride, U. S. P.) intravenously and found it to be excreted partly by the kidney and partly through the colon. After ligating segments of both small and large bowel in the cat, Taylor and Fine [157] found only a small amount of calcium was excreted through either of these portions of the bowel, most of it coming through the kidneys.

*Ileocecal Valve.*—A study of the physiology of the colon would not be complete without mention of the ileocecal valve or sphincter, and some of its functions. A comprehensive review of the literature will not be attempted, but merely a record of outstanding factors influencing or influenced by the large intestine. The importance of this sphincter is evidenced from the fact that certain observers have stated its proper function is just as essential to intestinal absorption as in the pylorus, and the former makes possible absorption of 95 per cent of the food before the cecum is reached. Alvarez quoted Rutherford and others as having observed in patients with cecal fistulas swaying movements associated with the to-and-fro contractions of the terminal portion of the ileum. About 4 cc. of semifluid feces came out of this sphincter in a jet every few moments; the lumen was enlarged and the circular fibers were relaxed. Viault and Jolyet [158] regard this act of the passage of excreta from the small into the large intestine as "internal defecation." Normally, this sphincter varied in tautness from the condition observed by Rutherford in which even a no. 12 French catheter could not be passed, to that observed by Short, in which he could easily insert his finger during relaxation. Macewen [159] was the first observer to be impressed with the sudden increase in activity of this sphincter after

156. Renon and Ricket, quoted by Peola: Gazz. d. osp. **46**:1181, 1925.

157. Taylor, N. B., and Fine, A.: Excretion of Calcium Through the Intestine, Am. J. Physiol. **93**:544 (June) 1930.

158. Viault and Jolyet, quoted by Luciani: Human Physiology, London, The Macmillan Company, 1913, vol. 2, p. 364.

159. Macewen, William: The Function of the Caecum and Appendix, Lancet **2**:995 (Oct. 8) 1904.

the taking of food, which Cannon [13] has shown initiates movements in the cecum and ascending colon. Hertz and Newton also saw that filling of the proximal portion of the large intestine generally took place passively and quite slowly, and in this manner, at times, considerable pressure was exerted when the chyme was forced through the sphincter. Berlatzky [160] and Hertz [44] noted great increase in the rate of passage of contents of the ileum into the colon with the taking of food.

*Ileocecal Sphincter.*—Alvarez observed that the function of this structure is to prevent the reflux of foul bacteria-laden contents of the colon, when absorption is slight, into the ileum where absorption is good, and to prevent too rapid passage of feces through the last segment of the small bowel. In event of the latter, no doubt diarrhea would often occur and symptoms of true auto-intoxication, whatever they may be, might be expected. As mentioned, the ileocecal sphincter is subject to reflexes such as the gastro-ileac or feeding reflex. Hinrichsen and Ivy [161] found that stimulation of the pyloric sphincter resulted in contraction of the ileocecal structure; likewise, distention of the stomach, duodenum, ileum or colon resulted in a similar action. In a large series of experiments they found that this sphincter may contract through either extrinsic or intrinsic mechanism. They found both motor and inhibitory fibers running to it from the vagus and motor fibers alone in the splanchnic system. Contraction of the sphincter resulted also from stimulation of both the hypogastric and pelvic nerves. They concluded that this is as true a sphincter as that of the pylorus, and that it stands in the same relation to the colon and small bowel as the pyloric sphincter does to the stomach and duodenum. The angle at which the ileocecal valve enters the colon has been the subject of much discussion because of the relationship it bears to intussuception. In cases in which there is disproportion in diameter of the two segments of bowel, along with excessive mobility, there is a tendency of the ileum to invaginate into the cecum.

This sphincter is no doubt of significance pathologically, both with reference to the digestive tract and the body in general. However, definite proof of a mechanism by which any influence of this nature takes place is lacking. Incompetence of the valve with regurgitation of the contents of the colon into the ileum has been blamed for many human ills, notably auto-intoxication, pernicious anemia, neurosis and epilepsy, yet, insufficiency of this sphincter seems to be present too often in normal individuals to lay the blame to such mechanism. Alvarez

160. Berlatzky, quoted by Luciani: Human Physiology, New York, The Macmillan Company, 1913, vol. 2, p. 366.

161. Hinrichsen, J., and Ivy, A. C.: Studies on the Ileo-Cecal Sphincter of the Dog, Am. J. Physiol. **96**:494 (Feb.) 1931.

stated that normally in about 60 per cent of the cases in which a barium enema is given some of it will run back into the ileum, and if the enema is big enough or the patient holds it long enough, it could always be made to flow back. This is certainly true of many of the laboratory animals, especially the dog. However, in the cat, this valve seems to be competent under considerable pressure, as Cannon,[11] Alvarez and others have noted. Weber [162] emphasizes the fact that distinction should be made between insufficiency and patency of the ileocecal valve. The former is found in practically all individuals when enough solution is introduced through the rectum, whereas patency usually occurs as a result of a pathologic condition, such as adhesions from chronic ulcerative colitis or chronic tuberculosis in that region. From a clinical standpoint, this distinction would seem of significance because it is almost invariably the rule that in cases of disease of the right third of the colon or of the terminal ileum, there is definite and sometimes severe secondary anemia. It would seem that there is more than a mere possibility that toxic substances could readily and constantly run back from the cecum, through the patent valve into the ileum, where absorption is notably facilitated. The sphincter seems to be a fairly efficient barrier to such regurgitation under normal conditions because great pressures are rarely present. However, a serious objection to this hypothesis lies in the fact that such anemia cannot be produced experimentally. In a series of dogs in which this valve was rendered incompetent by operative procedures, unusual variation in the hemoglobin and erythrocytes could not be detected in these animals during a period of fifteen months, in which estimations were made at least every ten days. It would seem that it is not possible to determine that insufficiency of this valve is of any etiologic significance in disease.

### INNERVATION OF THE COLON: COLONIC SECRETION

Section of nerves to the colon seems to influence the character and amount of secretion as well as the movements of that organ. The nerve supply also is of importance in the evaluation of the experiments presented in this study.

The extrinsic nerves of the colon are derived in general from the two portions of the vegetative nervous system. Broadly speaking, the sympathetic nerves reach the wall of the bowel through the hypogastric and inferior mesenteric nerves, and the parasympathetic nerves enter by way of the pelvic nerve or nervus erigentes. The former in general are inhibitory to the muscular coats of the wall of the bowel and motor to the internal anal sphincter, whereas the pelvic nerve is motor to the colon and inhibitory to the sphincter of the anus. Most investi-

162. Weber, H.: Personal communication to the authors.

gators are agreed that the vagus nerve takes little part in the innervation of the colon, yet there is some evidence, such as that by Boehm,[163] to suggest that in a few animals, the rabbit especially, the vagus does influence movements of the large intestine. The sympathetic innervation to the colon, according to Hovelacque,[164] is formed as follows: The superior mesenteric and semilunar ganglions surrounding the celiac axis supply the stomach, liver, spleen and small intestines and their blood vessels. Ganglions are also present adjacent to the renal arteries, the spermatic or ovarian vessels, which supply fibers proceeding along with vessels to the respective structures. The sympathetic nerves which pass to the colon have for their immediate origin the intercommunicating branches between the semilunar and celiac ganglions and the renal plexuses. The intermesenteric plexus descends in the median line and is joined on each side by the convergent branches from the first to the fourth lumbar ganglions, and these three roots form a more or less intricate plexus between the common iliac arteries called the presacral nerve (or plexus). In 20 per cent of cases the latter structure is a single nerve, and in 80 per cent it assumes a plexiform arrangement. At any rate, it descends into the pelvis and at the level of the first sacral vertebra divides into right and left hypogastric nerves, which join the corresponding ganglions where the cell stations of these fibers are situated. From there the postganglionic fibers of distribution pass to the pelvic viscera, lower part of the rectum and internal anal sphincter.

The inferior mesenteric nerves (sympathetic) supplying the greater part of the colon are formed as follows: Immediately below the level of the origin of the inferior mesenteric artery a large branch leaves the intermesenteric plexus of each side and passes inward on the aorta to reach the artery about 1.5 cm. from its origin. Finally, these two trunks unite and give rise to three or four large branches which course along the lateral borders of the vessels. They do not form a very close network around the vessel, nor are they closely attached to the vessel. From these nerves subsidiary trunks arise at the levels of the main divisions of the arteries and anastomose with one another in avascular parts of the mesosigmoid. From this network the final nerves of distribution are derived; their slender filaments cross juxtacolic vascular arcades and enter the wall of the bowel between the terminal branches of the vessels.

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163. Boehm, Gottfried: Ueber den Einfluss des Nervus vagus auf den Dickdarm, München. med. Wchnschr. **59**:1476 (July 2) 1912; Ueber den Einfluss des Nervus sympathicus und anderer autonomer Nerven auf die Bewegungen des Dickdarms, Arch. f. exper. Path. u. Pharmakol. **72**:1 (April 24) 1913.

164. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du système grand sympathique chez l'homme, Paris, G. Doin & Cie, 1927.

Two or three large branches accompany the superior hemorrhoidal artery and invest the lateral and posterior walls in a plexiform manner. The distributions of the inferior mesenteric nerves correspond to those of the artery of the same name, and toward the end of the transverse colon where the left colic artery anastomoses with the middle colic branches of the inferior mesenteric plexus they communicate with filaments derived from the superior mesenteric plexus. The sympathetic innervation of the remainder of the colon is in dispute. Carlson [165] and also Cannon [11] are of the opinion that the transverse colon has no extrinsic nerves.

Whether the lumbar fibers which join the inferior mesenteric plexus to form the sacral nerve actually contribute functionally to the plexus is also disputed, and according to Learmonth and Braasch [166] is a question of great significance surgically in the treatment of Hirschsprung's disease. If they do not, as Delmas and Laux [167] hold, then lumbar ramisectomy and ganglionectomy, the operation favored by Hunter [168] and Royle [169] and by Judd and Adson,[170] would affect only that portion of the bowel innervated by the presacral nerve (lower part of the rectum and internal anal sphincter). But if they do contribute functionally, as Hovelacque contends, then the descending and sigmoid portions of the colon as well as the rectum and internal sphincter of the anus would be affected. Clinical experience favors the latter view.

In adult human beings there is no inferior mesenteric ganglion, although in the fetus and in the child it has occasionally been identified. When present, it is situated at the juncture of the two parts of the intermesenteric plexus after they have given off nerves to the colon. In the dog there is a definite inferior mesenteric ganglion and from this

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165. Carlson, A. J.: The Extrinsic Nervous Control of the Large Bowel, J. A. M. A. **94**:78 (Jan. 11) 1930.

166. Learmonth, J. R., and Braasch, W. F.: Resection of Presacral Nerve in the Treatment of Cord Bladder: Preliminary Report, Surg., Gynec. & Obst. **51**: 494 (Oct.) 1930.

167. Delmas, J., and Laux: Constitution, forme et rapports du nerf présacré, Montpellier méd. **49**:187 (May 1) 1927.

168. Hunter, J. I.: The Postural Influence of Sympathetic Innervation of Voluntary Muscle, M. J. Australia **1**:86 (Jan. 26) 1924; The Significance of the Double Innervation of Voluntary Muscle Illustrated by Reference to the Maintenance of the Posture of the Wing, ibid. **1**:581 (June 14) 1924; On the Choice of Procedure Adopted in the Operation of Ramisection for Spastic Paralysis, ibid. **1**:590 (June 14) 1924.

169. Royle, N. D.: The Operations of Sympathetic Ramisection, M. J. Australia **1**:587 (June 14) 1924.

170. Judd, E. S., and Adson, A. W.: Lumbar Sympathetic Ganglionectomy and Ramisectomy for Congenital Idiopathic Dilatation of the Colon, Ann. Surg. **88**:479 (Sept.) 1928.

ganglion pass the lumbar colonic nerves accompanying the inferior mesenteric artery and its branches.[171]

The internal anal sphincter in man is innervated by the thoracicolumbar outflow in one or both of the following ways, according to Learmonth and Markowitz:[171] (1) by way of the inferior mesenteric nerves through the superior hemorrhoidal branches and branches from the hypogastric ganglions and (2) by way of the presacral nerve.

In dogs impulses pass from the inferior mesenteric ganglion through the lumbar colonic nerves or through the hypogastric nerves to this sphincter.

Bayliss and Starling[7] claim that the functional activity of the sympathetic nervous system to the distal part of the colon and rectum is unquestionably inhibitory. However, there is some doubt as to the nature of the impulses to the proximal part of the colon. Carlson stated that the hypogastric fibers to the ascending and transverse colon may be both inhibitory and motor in type, and the result of stimulation depends on the tonus or motor state of the bowel at the time of stimulation. That is, if the colon is atonic to begin with, stimulation will cause a powerful contraction, but if it is in a fair degree of tonus or rhythmic contraction, the tonus or mobility is decreased. This is true of dogs, but not necessarily so of man. Leman[172] agreed to this view, stating further that the depressor effect of these nerves occurs only in the presence of definite tonus of the musculature, and if such tonus is absent no demonstrable effect occurs from stimulation. The mechanism of this effect may possibly be a contraction of the vessels of the intestine. Ludlum and McDonald,[173] from studies on the movements of the colon by roentgenoscopy, and after atropinization, came to a similar conclusion, stating that the amplitude and postural tone of the large intestine are probably dependent on vagus sympathetic balance and may be altered by chemical substances such as atropine and physostigmine (eserine). Their studies, however, do not seem clearcut in that they do not take into account the range of normal movements of the colon. The sympathetic outflow to the internal anal sphincter is largely motor, according to Scott and Morton,[174] and stimulation of the right or left hypogastric nerves or the lumbar colonic nerve will cause con-

171. Learmonth, J. R., and Markowitz, J.: Studies on the Function of the Lumbar Sympathetic Outflow: I. The Relation of the Lumbar Sympathetic Outflow to the Sphincter Ani Internus, Am. J. Physiol. **89**:686 (Aug.) 1929; Studies on the Innervation of the Large Bowel: II. The Influence of the Lumbar Colonic Nerves on the Distal Part of the Colon, ibid. **94**:501 (Sept.) 1930.

172. Leman, A. E.: Present Status of the Question of Peripheral Innervation of the Colonic Movements, Kazan. med. zh. **13**:171, 1930.

173. Ludlum, S. D., and McDonald, Ellice: The Large Intestine and Vagus Sympathetic Action by Atropin and Eserine, M. J. & Rec. **123**:228 (Feb. 17) 1926.

174. Scott, W. J. M., and Morton, J. J.: Sympathetic Inhibition of the Large Intestine in Hirschsprung's Disease, J. Clin. Investigation **9**:247 (Oct.) 1930.

tractions of that muscle. There are a few inhibitory fibers, as Learmonth and Markowitz [171] have shown, which has been demonstrated by the use of ergotoxin, a drug that paralyzes motor sympathetic fibers.

*Motor Nerves.*—The motor innervation of the colon is derived from the parasympathetic system through the pelvic nerves. The latter are formed by the union of the fibers of the anterior primary divisions of either the second, third or fourth sacral nerve which then divide into anterior and posterior branches, the posterior traversing, but not forming synapses in, the hypogastric ganglia, as do the hypogastric nerves. The posterior branch then reaches the surface of the large bowel in a plexiform manner, and this is similar to part of Auerbach's plexus of the small intestine. The latter, however, lies between the two layers of muscle. The anterior branch of the pelvic nerve reaches and innervates the bladder in an identical manner.[171]

Stimulation of the pelvic nerve results in contraction of both the circular and the longitudinal musculature; in the dog this makes the colon look like a cord. The nerve tires easily. Again, Carlson claims that these nerves supply only the distal segment and the cecum and ascending portions of the colon. He and Cannon [11] are inclined to believe that the transverse colon receives no extrinsic nerves. Leman, however, claimed from his studies that each muscle of the large intestine receives fibers from the sympathetic and from the parasympathetic system.

One would naturally expect the distal part of the colon to have a more potent motor innervation because of the physiology of that portion of the bowel and its better developed musculature, present for the purpose of strong contractions to evacuate the bowel. On the right side, or proximal part, of the colon where the contents are liquid and absorption is taking place, peristalsis and backward running waves of constriction are all the movements that ordinarily take place.

The internal anal sphincter relaxes on stimulation of the pelvic nerves according to Gaskell,[175] Bartle [176] and others, although the hypogastric nerves contain a few inhibition fibers, as Leman has stated. The depressor action of the sacral nerves is not limited to the sphincter but also extends to the adjacent portion of the rectum, and so the lower part of the rectum probably contains both types of fibers. Further stimulation of the peripheral segment of the divided sacral nerve leads to contraction of the lower segment of the rectum.

Clinically, the innervation of the colon is of importance in the treatment of Hirschsprung's disease and other types of idiopathic dilatations

175. Gaskell, W. H.: The Involuntary Nervous System, London, Longmans, Green & Co., 1920.

176. Bartle, H. J.: Megacolon: A Résumé of the Literature and Report of a Case; Ramisection Proposed as a Form of Treatment, Am. J. M. Sc. **171**:67 (Jan.) 1926.

of the colon.[177] By interruption of the inhibitory impulses through cutting the presacral nerve, or by lumbar ramisectomy and ganglionectomy, the motor nerves are left in less disputed control, and at the same time the opposition to the expulsion of the contents of the bowel offered by the internal anal sphincter is removed.

That the nervous system does influence the secretion of mucus in situations other than in the colon is no doubt true. Barrington,[178] by stimulation of the hypogastric nerve of a cat, obtained increased secretion of mucus from Bartholin's glands. He considered the gland to be situated deeply enough so that it was not influenced by events taking place in nearby viscera. Moreover, as is true with the salivary gland, psychic influences are capable of inciting secretion of the gland. The large amounts of mucus present in mucous colitis may be due to the intervention of the nervous system analogous to that found in the salivary and Bartholin's glands, but this point is still in doubt. It is also stated that it is hardly relevant to argue from one case to another, owing to different anatomic relationships and histologic appearance of the mucus cells in the various situations.

In a careful study, Florey[179] found that stimulation of either the sympathetic or the parasympathetic nerves was without effect on the amount of mucus secreted by the colon. He used Thiry fistulas made in the central portion of the distal end of the large intestine, and by biopsy several months after the operation found that the mucosa was indistinguishable from the normal. He also used a patch of colon entirely separated from the mesentery, and this continued to secrete mucus as it would ordinarily. In another series of experiments he tried to demonstrate nerve fibers to the mucus-secreting cells by many different methods but was unable to do this, concluding that these cells had no nerve fibers coming to them because by the same methods he could see innervating fibers to other glandular tissues, such as the pancreas and salivary glands. Florey summarized the evidence against nervous control of the goblet cells as follows: (1) The secretion of mucus is normal after section of nerves to the colon; (2) the secretion of mucus from a Thiry fistula is small and at a constant rate; (3) tissue cultures from chicken intestine show goblet cells developing and producing mucus; (4) on histologic examination nerves are not demonstrated, as in the case of the salivary glands, and (5) colonic secretion

177. Rankin, F. W., and Learmonth, J. R.: Section of Sympathetic Nerves of the Distal Part of the Colon and the Rectum in the Treatment of Hirschsprung's Disease and Certain Types of Constipation, Ann. Surg. **92**:710 (Oct.) 1930.

178. Barrington, F. J. F.: The Variations in the Mucin Content of the Bulbo-Urethral Glands, Internat. Monatschr. f. Anat. u. Physiol. **30**:1, 1914.

179. Florey, H.: The Secretion of Mucus by the Colon, Brit. J. Exper. Path. **11**:348 (Oct.) 1930.

is not obtained from stimulation of nerves. In this connection Florey commented that the increased amounts of mucus seen in mucous colitis do not seem to be due to nervous excitation. He is of the opinion that increased secretion of mucus is due to injury to cells resulting either from direct trauma to the goblet cells or from liberation of a chemical substance which stimulates the goblet cells. However, Wood,[180] by sectioning the vagi, obtained decreased amounts of secretion in both small and large intestines even after administration of purgatives, but Hay [129] stated that this could not be, as he claimed not to have obtained a change after section of nerves. Moreau divided the mesenteric sympathetic nerves and thought he obtained increased amounts of mucus from the bowel. Hay interpreted these observations as due to an inhibiting action of the sympathetic system on secretion and an excitatory action on absorption, the total quantity depending on a balance between the nerves. Any influence which may increase or lessen purgative action may do this by affecting the rate of secretion or absorption.

Heupke [181] summarized the present knowledge of the secretion and excretion of the colon. Using a Thiry-Vella type of fistula on a dog, he found inorganic components such as potassium, calcium, magnesium and phosphoric acid always present, and these made up about 25 per cent of the total weight of dried secretion; 75 per cent was made up of organic compounds, mainly mucus, but also small quantities of purine bases and occasionally amino-acids. Urea, creatinine, cholesterol, and indole, skatol and other products of putrefaction were not present. Fermentative action was so slight that for practical purposes it can be disregarded. Of eleven coal tar dyes, given by subcutaneous or intravenous routes, none was excreted by the colon, and by the use of medicaments in a similar manner, it was found that iodine, bromine and potassium thiocyanate were recovered in small amounts in the isolated colon. Potassium ferrocyanide, quinine and gallic acid were not recovered from the secretion of the colon.

Some work which we have done on the secretory activity of the colon of the dog, isolated within the abdominal cavity, will be reported in a subsequent paper. Therein reference will be made to work of Drury, Florey and Florey, Hertz, Cook and Schlesinger,[182] Florey, and Harvey.[183]

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180. Wood, H. C.: On the Influence of Section of the Cervical Pneumogastrics upon the Action of Emetics and Cathartics, Am. J. M. Sc. **60**:75 (July) 1870.

181. Heupke, W.: Ueber die Sekretion und Excretion des Dickdarms, Ztschr. f. d. ges. exper. Med. **75**:83, 1931.

182. Hertz, A. F.; Cook, F., and Schlesinger, E. G.: The Action of Saline Purgatives, Proc. Roy. Soc. Med. (Sect. Therap. & Pharmacol.) **2**:21, 1908-1909.

183. Harvey, R. W.: Variations in the Wall of the Large Intestine and in the Number and Staining Properties of the Goblet Cells, Anat. Rec. **2**:129 (July) 1908.

# TREATMENT OF SECONDARY ANEMIA IN GYNECOLOGIC PATIENTS

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Secondary anemia following excessive uterine hemorrhage constitutes a frequent and important complication of gynecologic disorders. When the bleeding is the result of such gross lesions as uterine fibroids, a severe degree of anemia may present a situation requiring considerable delicacy of judgment in its handling. A major surgical procedure is usually necessary to stop the excessive flow effectively and permanently, and before the surgeon is justified in operating the anemia must be effectively treated to an extent sufficient to render the procedure a safe risk; this must usually be accomplished in the all too brief interval between two prolonged and profuse menstrual periods. It is therefore essential that one have at one's disposal efficient and speedy methods of effecting such an improvement.

For many years iron in one form or another has been the standard drug used in the treatment of such conditions, and more recently transfusion has proved to be of tremendous help. The past six years, however, have constituted a period of flux in the treatment of secondary anemia, stimulated largely by the epoch-making work of Minot and Murphy in the treatment of pernicious anemia with liver and liver extracts. So enthusiastic has been the acceptance of liver as a panacea, and so widespread its adoption in the treatment of various types of anemias, that it has quickly risen from a lowly position as one of the butcher's cheaper wares to that of an expensive drug, thus economically handicapping the victims of primary anemia to whom its use is essential.

Is this indiscriminate use of liver essential? It seems time to pause and compare carefully the results of liver therapy with those obtained by other methods, and at the same time, if possible, determine the speediest and most efficient method at one's disposal. In an attempt to do this I have reviewed and analyzed the records of all patients admitted to the gynecologic service of the Johns Hopkins Hospital from Jan. 1, 1926, to May 1, 1931, in whom the hemoglobin on admission was 50 per cent or below. There were 305 such patients, constituting 4.6 per cent of the 6,570 total admissions to the service during the same period. Of these, 233 were colored and 72 were white in a service that admits about equal numbers of the two races.

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The degree of anemia in these 305 patients is indicated in table 1.

The lowest amount of hemoglobin in the series was 10 per cent. This patient was suffering from an advanced inoperable carcinoma of the cervix; she was given a blood transfusion and was discharged with a hemoglobin of 35 per cent after seventeen days on a liver diet and pills of ferrous carbonate, U. S. P. The cervix was cauterized to control the bleeding, but the patient was considered by both surgeons and radiologists to be beyond the stage of possible real benefit either from surgery or irradiation.

### ETIOLOGY OF ANEMIA

Table 2 shows the relative frequency of the various gynecologic disorders which had preceded the anemia. This table requires only

TABLE 1.—*Distribution of Patients According to Degree of Anemia*

| Hemoglobin, per Cent (Sahli) | Number of Patients |
|---|---|
| 10-20 | 16 |
| 21-30 | 44 |
| 31-40 | 81 |
| 41-50 | 164 |

TABLE 2.—*Frequency of Various Gynecologic Conditions Which Acted as Contributing Causes of Anemia*

| Diagnosis | Number of Cases |
|---|---|
| Myomata uteri | 138 |
| Endometrial hyperplasia and bleeding without determined anatomic lesion | 57 |
| Carcinoma of the cervix | 27 |
| Other malignant conditions | 19 |
| Pelvic inflammatory disease | 24 |
| Tubal pregnancy | 11 |
| Incomplete abortion | 9 |
| Tuberculosis of pelvic organs and peritoneum | 4 |
| Tuberculosis of the kidney | 1 |
| Miscellaneous diagnoses | 15 |

brief comment. As would be expected, uterine myomas with associated bleeding due to submucous nodules constitute by far the largest group. Endometrial hyperplasia and similar conditions, because of the absence of any gross pathologic lesion, are not as a rule considered serious, but it is seen here that they are probably the etiologic factors in the second largest group of anemias. The 19 patients with malignant conditions other than carcinoma of the cervix include 2 with adenocarcinoma of the body of the uterus, 3 with sarcomatous degeneration of myomas, 4 with hypernephroma and 3 with carcinoma of the bladder. All these showed external loss of blood, either through excessive uterine bleeding or hematuria, in addition to general debility from the disease. In the other patients, 5 with carcinoma of the ovary, 1 with pseudomyxoma peritonei and 1 with carcinoma of the tube, the anemia was merely one of the many manifestations of the ravages of the disease.

The 24 patients listed as suffering from pelvic inflammatory disease all afforded examples of the severer forms of this condition such as pelvic abscess, tubo-ovarian abscess and pelvic peritonitis. In some of these bleeding was a factor, but in the majority the anemia was largely a part of the general debility associated with a severe inflammation. The same was true of the tuberculous patients. Pelvic inflammatory disease in the chronic form was also associated with many of the

TABLE 3.—*Diagnosis, Per Cent of Hemoglobin and Operation in Fatal Cases*

| Diagnosis | Hemoglobin, per Cent | Operation | Cause of Death |
|---|---|---|---|
| 1. Recurrent carcinoma of cervix; ureteral obstruction | 30 | None | Uremia |
| 2. Pseudomyxoma peritonei ..... | 50 | Exploratory laparotomy | Shock |
| 3. Sloughing submucous myoma; bilateral femoral thrombophlebitis | 33-16 | Vaginal myomectomy | Phlebitis |
| 4. Adenocarcinoma of corpus uteri..... | 50 | Panhysterectomy | Shock |
| 5. Myomata uteri; intracranial hemorrhage | 25 | None | Intracranial hemorrhage |
| 6. Infected myoma; pulmonary emboli; lung abscess | 30 | None | Transfusion reaction |
| 7. Sarcoma of ovary..... | 50 | Exploratory laparotomy | Shock |
| 8. Myoma; sarcomatous degeneration with metastases | 40 | None | |
| 9. Carcinomatosis; adenocarcinoma of ovary | 50-57 | Exploratory laparotomy | Shock |
| 10. Tuberculous salpingitis and peritonitis; pulmonary tuberculosis | 50 | Exploratory laparotomy | |
| 11. Myomata uteri; bilateral tubo-ovarian abscess | 50-58 | Hysterectomy; bilateral salpingo-oophorectomy | Pneumonia; peritonitis |
| 12. Recurrent carcinoma of ovary; carcinomatosis | 50 | None | |
| 13. Pelvic abscess communicating with sigmoid; generalized peritonitis | 50 | Posterior colpotomy | Infection; inanition |
| 14. Nephrolithiasis; pyonephrosis ..... | 35 | Nephrectomy | Collapse |
| 15. Tuberculous salpingitis and peritonitis.. | 39-28 | Posterior colpotomy | Pneumonia |
| 16. Myomata uteri; peculiar infection of uterus and pancreas | 25 | None | Intracranial hemorrhage |

myomas but was not usually considered an important factor in the production of the anemia, for this was directly attributable in most cases to bleeding from a submucous myomatous nodule.

## SURGICAL TREATMENT AND RESULTS

Dr. Thomas S. Cullen, in 1913, reported the cases of 170 patients with a hemoglobin of 40 per cent or below treated in the gynecologic service up to that time. Among these 170 patients there were 20 deaths, but in 7 of these cases no operation was performed, the condition being considered hopeless, and in 9 others the operation was for an advanced

malignant condition, so that the mortality was for the most part among absolutely hopeless cases. In the present series of 305 patients all but 33 underwent some form of operation. There were 147 laparotomies, usually for hysterectomy, 119 minor procedures, among which are included vaginal removal of submucous myomas, and 6 operations on the kidney. On discharge, 146 patients were well, 126 improved and 17 unimproved, and there were 16 deaths. Many of the patients classified as improved might have been considered well except for the fact that it is a conservative rule of the service to classify as improved patients suffering from such conditions as endometrial hyperplasia in which the symptoms are apt to recur.

The 16 deaths give a mortality for the series of 5.25 per cent as compared with a total mortality in the service during the same period of 1.83 per cent. The majority of the deaths, however, were in patients in an absolutely hopeless condition on entering the hospital, 5 of whom

TABLE 4.—*Postoperative Complications*

| Complication | No. of Cases | Complication | No. of Cases |
|---|---|---|---|
| Hyperpyrexia | 11 | Secondary hemorrhage | 2 |
| Bronchopneumonia | 8 | Fecal fistula | 1 |
| Thrombophlebitis | 7 | Hemiplegia | 1 |
| Pyelitis | 6 | Intestinal obstruction | 1 |
| Shock | 4 | Peritonitis | 1 |
| Infected incision | 3 | Cystitis | 1 |
| Pelvic abscess | 2 | | |

could not be operated on, as will be seen by reference to table 3. There were 2 patients, numbers 3 and 14 in the table, in whom perhaps transfusion might have been of life-saving benefit, but in each of these instances every possible effort was made to obtain suitable donors without success.

### POSTOPERATIVE COMPLICATIONS

Postoperative complications, particularly thrombophlebitis, occurred less frequently in this series than I had anticipated. In gynecologic operations at this hospital we are constantly on the lookout for this complication, and particularly so among the anemic patients, and I was rather surprised to find that it occurred only 7 times in the 305 cases. Table 4 shows the relative frequency of various postoperative complications in the series.

### TREATMENT OF ANEMIA

The use of liver for secondary anemia was begun in the service in the fall of 1926 by Dr. R. Glen Craig, the resident at that time. Prior to this the treatment had been the administration of a nourishing, high caloric diet, with elixir of iron, quinine and strychnine to stimulate the

appetite, and pills of ferrous carbonate from 10 to 15 grains (0.65 to 0.972 Gm.) three times a day. Transfusions were also frequently employed. Liver then came into vogue and was used in quantities of 200 Gm. a day added to a diet similar to that previously used. In a small series of cases no iron was used in order to determine accurately, if possible, the beneficial effect of liver per se, but in the majority of the cases in my series iron, quinine and strychnine and pills of ferrous carbonate have also been given. For the first few months after the introduction of liver, transfusions were used less frequently, but because of their unquestioned effectiveness, and particularly because of their

TABLE 5.—*Changes in the Percentage of Hemoglobin Following the Several Types of Treatment*

| Treatment | Number of Cases | Average Rise in Hemoglobin, per Cent | Average Number of Days |
|---|---|---|---|
| None | 21 | 2 | 22 |
| Amplified diet; iron, quinine and strychnine; pills of ferrous carbonate | 8 | 25 | 26 |
| Liver diet; iron, quinine and strychnine; pills of ferrous carbonate | 22 | 20 | 24 |
| Liver diet without iron | 12 | 10 | 25 |
| Transfusion alone | 6 | 14 | 8 |
| Two transfusions | 12 | 37 | 18 |
| Transfusion; amplified diet; iron, quinine and strychnine; pills of ferrous carbonate | 15 | 22 | 19 |
| Transfusion; liver diet; iron, quinine and strychnine; pills of ferrous carbonate | 27 | 24 | 21 |
| Liver extract; iron, quinine and strychnine; pills of ferrous carbonate | 13 | 18 | 19 |
| Transfusion; liver extract; iron, quinine and strychnine; pills of ferrous carbonate | 10 | 25 | 20 |
| Iron ammonium citrate | 6 | 15 | 16 |
| Transfusion; iron ammonium citrate | 4 | 24 | 19 |
| Severe infection or advanced malignant condition treated without transfusion | 29 | 2 | 28 |
| Severe infection or advanced malignant condition treated with transfusion | 12 | 13 | 28 |

importance as a time-saving factor, their use, wherever possible, was quickly resumed. Within the last two years liver has been replaced to some extent by liver extract given in quantities of 30 cc. three times a day.

Beginning about Oct. 1, 1930, Dr. Beebe and Dr. Wintrobe of the medical service, who were studying secondary anemias in general, treated a small series of gynecologic patients with iron ammonium citrate, 2 cc. of the crystals dissolved in a glass of milk three times a day.

Table 5 shows in composite form the results obtained with these various forms of treatment. Of the 305 cases, 197 were used in compiling this table. In the other cases the period of observation was too brief or the number of hemoglobin determinations too few to admit of accurate conclusions. I must emphasize the fact that the figures are all averages and should not be taken too literally, but with this reser-

vation in mind the following conclusions may be drawn: Some form of special treatment seems to be necessary to obtain a rise in hemoglobin. In the 21 patients not treated for anemia, that is, who were put on ordinary ward diet without administration of iron, there was practically no average rise in hemoglobin over an average period of twenty-two days. The older treatment with a nourishing high caloric diet in combination with iron, quinine and strychnine and pills of ferrous carbonate apparently gave as good results as were later obtained with the addition of liver or liver extract. Liver without iron was less than half as efficient as all forms of diet with iron. All forms of diet with iron succeeded in raising the average of the hemoglobin slightly less than 1 per cent a day, while the same types of treatment with transfusion raised the hemoglobin in each case a little more than 1 per cent a day. A single transfusion in 6 cases is seen to have produced a rise of almost 2 per cent a day, while with two transfusions there was a rise of more than 2 per cent a day. The chief asset of transfusion in the cases of simple bleeding, therefore, seems to be a time-saving element. In fact, if the 14 per cent average rise in hemoglobin following transfusion alone had been based on determinations made the day before and the day after transfusion, the whole rise would probably have been found to occur during this period, but the average of eight days represents the time consumed after admission before a suitably matched donor with a negative Wassermann reaction could be obtained. This difficulty in securing donors is frequently encountered for colored patients. Similarly, those patients who had two transfusions were admitted with profound anemia, and on an average eighteen days were consumed in preparing for and giving two transfusions and other stimulative measures before any operative procedure was considered to be advisable.

The last two items of table 5 show strikingly the value of transfusion in combating the anemia resulting from wasting debilitating diseases. Here it was found to be the only method that was effective to any appreciable degree.

The accompanying charts represent graphically the results in specific cases of several of the foregoing methods of treatment. The charts are for the most part self-explanatory, but it may be stated that in the patient represented in chart 8 the secondary hemorrhage followed removal of the skin sutures on the eighth day following operation. This is an example of the fact frequently observed that healing proceeds more slowly in anemic patients, and serves to emphasize the fact that greater care and delay should be exercised in removal of the sutures in this type of case.

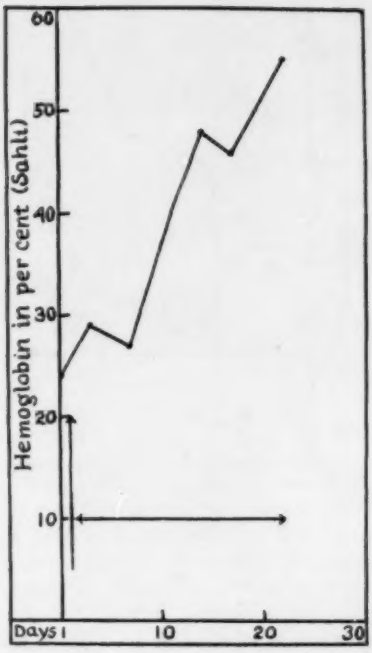


Chart 1 (unit no. 1824).—Rise in hemoglobin produced by a high caloric diet and iron. The patient was admitted on Jan. 4, and discharged on Jan. 27, 1927. The diagnosis was metrorrhagia and cervical polyp. Dilatation and curettage were performed. The vertical arrow indicates the date of operation; the horizontal arrow, the period over which the patient received a 4,000 calory diet, elixir of iron, quinine and strychnine, 8 cc. three times a day, and pills of ferrous carbonate, 0.3 Gm. three times a day.

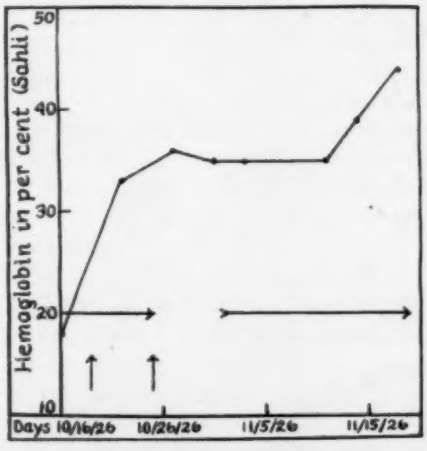


Chart 2 (unit no. 8328).—Effect on hemoglobin of transfusion and of a liver diet without iron. The patient was admitted on Oct. 16, and discharged on Nov. 19, 1926. The diagnosis was myomas of the uterus. Hysteromyomectomy was performed. The two horizontal arrows indicate the periods over which the patient received a Murphy-Minot diet; the first vertical arrow, the date of transfusion of 550 cc. of citrated blood, and the second vertical arrow, the date of operation.

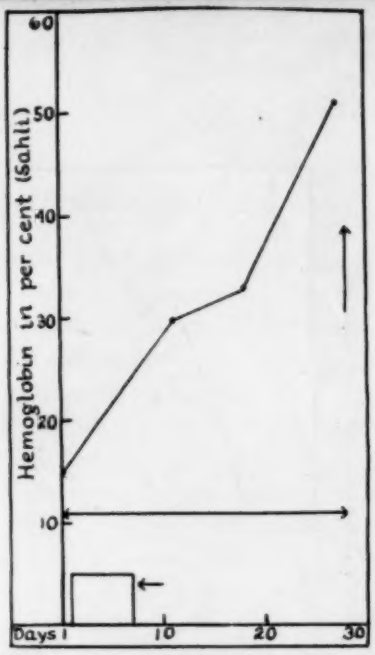


Chart 3 (unit no. 23985).—Effect on hemoglobin of a liver diet and iron. The patient was admitted on April 2, and discharged on May 20, 1929. The diagnosis was myomas of the uterus with submucous nodule. Panhysteromyomectomy and bilateral salpingo-oophorectomy were performed. The horizontal arrow indicates the period over which the patient received an amplified diet with 150 Gm. of liver daily, elixir of iron, quinine and strychnine, 5 cc. three times a day, and pills of ferrous carbonate, 1 Gm. three times a day; the block in the lower left corner, a daily hypodermic injection of 1 cc. of sodium cacodylate, and the vertical arrow, the date of operation.

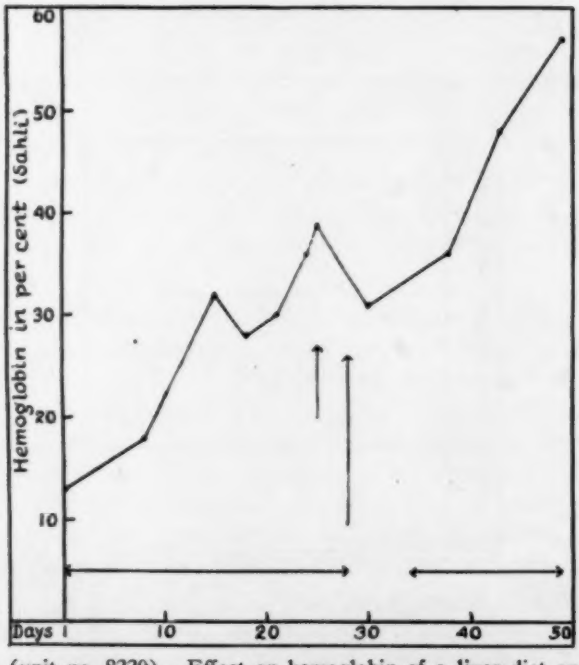


Chart 4 (unit no. 8220).—Effect on hemoglobin of a liver diet and iron. The patient was admitted on Oct. 11, and discharged on Dec. 1, 1926. The diagnosis was myomas of the uterus. Hysteromyomectomy, right salpingo-oophorectomy and appendectomy were performed. The horizontal arrows indicate the periods over which the patient received Murphy-Minot diet and pills of ferrous carbonate, 0.3 Gm. three times a day; the first vertical arrow, the onset of profuse menstruation, and the second vertical arrow, the date of operation.

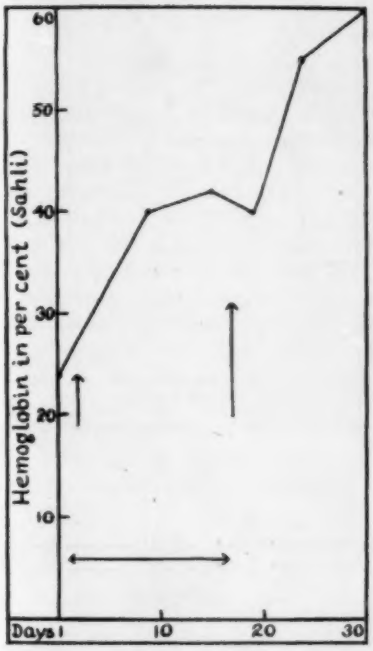


Chart 5

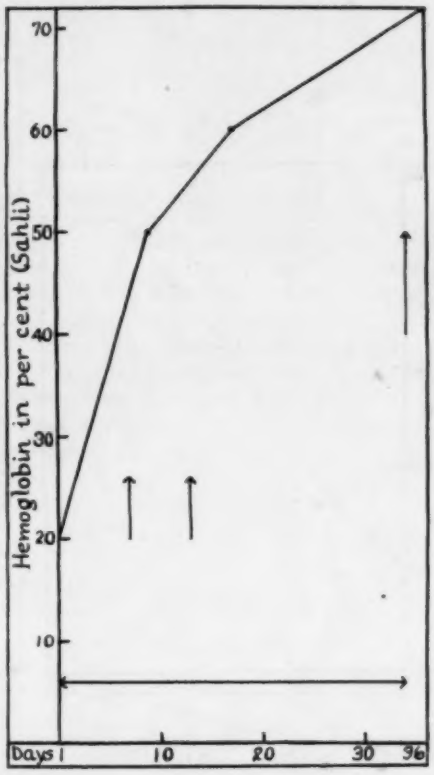


Chart 6

Chart 5 (unit no. 4787).—Effect on hemoglobin of transfusion, amplified diet and iron. The patient was admitted on May 12, and discharged on June 17, 1926. The diagnosis was myomas of the uterus. Hysteromyomectomy and left salpingo-oophorectomy were performed. The horizontal arrow indicates the period over which the patient received an amplified diet with elixir of iron, quinine and strychnine, 4 cc. three times a day, and pills of ferrous carbonate, 0.3 Gm. three times a day; the first vertical arrow, transfusion of 400 cc. of citrated blood, and the second, the date of operation.

Chart 6 (unit no. 34377).—Effect on hemoglobin of two transfusions, liver extract and iron. The patient was admitted on Dec. 2, 1930, and discharged on Jan. 24, 1931. The diagnosis was myomas of the uterus, chronic salpingitis and cardiac hypertrophy. Hysteromyomectomy, left salpingo-oophorectomy and appendectomy were performed. The first two vertical arrows indicate transfusions of citrated blood, 650 cc. each; the horizontal arrow, the period over which the patient received liver extract, 30 cc. twice daily, elixir of iron, quinine and strychnine, 5 cc. three times a day before meals, and pills of ferrous carbonate, 0.6 Gm. three times a day after meals, and the third vertical arrow, the date of operation.

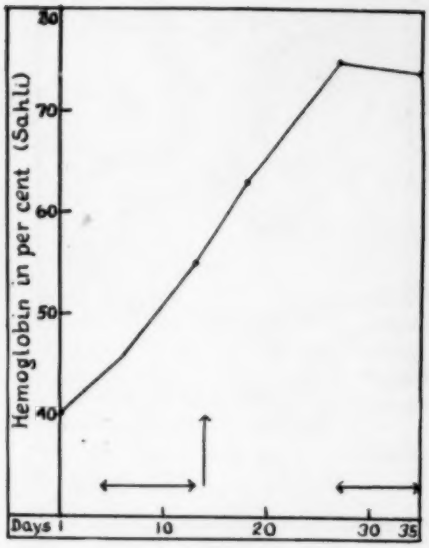


Chart 7

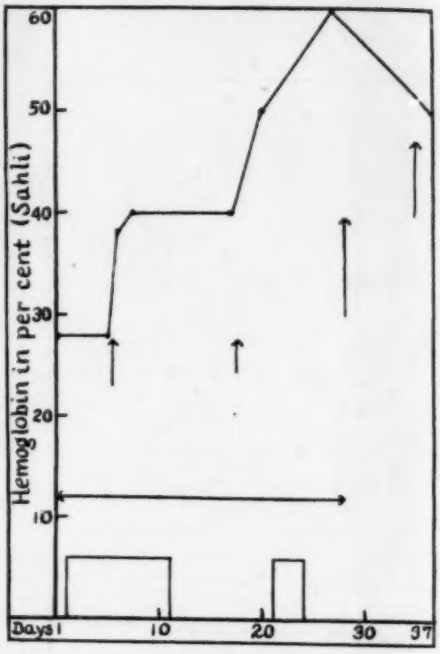


Chart 8

Chart 7 (unit no. 12587).—Effect on hemoglobin of iron ammonium citrate. The patient was admitted on Dec. 2, 1930, and discharged on Jan. 7, 1931. The diagnosis was myomas of the uterus. Hysteromyomectomy and appendectomy were performed. The patient received 2 cc. of crystals of iron ammonium citrate dissolved in a glass of milk three times a day over the periods indicated by the horizontal arrows. The date of operation is indicated by the vertical arrow.

Chart 8 (unit no. 26672).—This chart illustrates in a striking manner the inefficiency of dietary and medicinal treatment as compared with transfusion in cases complicated by infection. The patient was admitted on Sept. 3, and discharged on Oct. 27, 1929. The diagnosis was myomas of the uterus and tubo-ovarian abscess (right). Hysteromyomectomy and bilateral salpingo-oophorectomy were performed. The horizontal arrow indicates the period over which the patient received an amplified diet with 150 Gm. of liver daily and pills of ferrous carbonate, 1 Gm., three times a day; the two blocks at the bottom of the chart, the daily hypodermic administration of 1 cc. of sodium cacodylate; the first two vertical arrows, transfusions of 650 and 800 cc. of citrated blood. Note the sharp rise following each of these with the practically flat curve between the two. The third vertical arrow indicates the date of operation, and the fourth, a secondary hemorrhage necessitating a secondary closure of the abdominal incision and accounting for the fall in hemoglobin at the end of the chart.

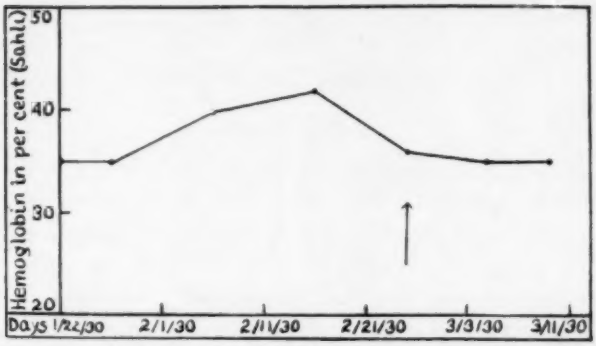


Chart 9 (unit no. 27363).—The inadequacy of dietary and medicinal treatment in a patient in whom the anemia was due to infection rather than hemorrhage. The patient was admitted on Jan. 22, and died on March 11, 1930. The diagnosis was left nephrolithiasis and pyonephrosis. Left nephrectomy was performed. The patient died of shock on the day of operation. The patient received an amplified diet with 200 Gm. of liver daily with elixir of iron, quinine and strychnine, 5 cc. three times a day before meals, and pills of ferrous carbonate, from 0.6 to 1 Gm. three times a day throughout her course in the hospital. The arrow indicates the time when the dosage of ferrous carbonate was increased to 1 Gm.

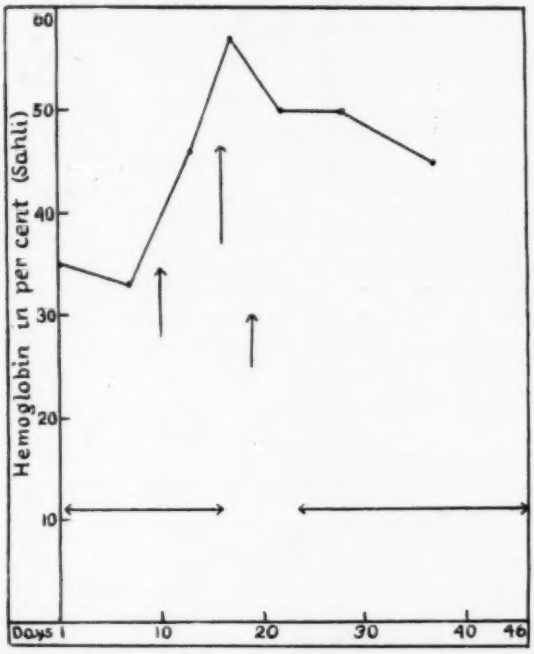


Chart 10 (unit no. 20713).—Detrimental effect on rise in hemoglobin produced by thrombophlebitis. The patient was admitted on Sept. 17, and discharged on Nov. 2, 1928. The diagnosis was myomas of the uterus and chronic salpingitis. Hysteromyomectomy, bilateral salpingo-oophorectomy and appendectomy were performed. The two horizontal arrows indicate periods over which the patient received an amplified diet with 200 Gm. of liver daily, elixir of iron, quinine and strychnine, 5 cc. three times a day, and pills of ferrous carbonate, 0.3 to 1 Gm. three times a day. The first vertical arrow indicates transfusion of 500 cc. of citrated blood; the second vertical arrow, operation and simultaneous transfusion of 460 cc. of citrated blood, and the third vertical arrow, the onset of the thrombophlebitis.

## CONCLUSIONS

From the study of the foregoing figures, I believe that the following conclusions are justified:

1. Secondary anemia, though a frequent and often annoying complication in gynecologic surgery, by careful preoperative and postoperative treatment may be rendered relatively innocuous so far as any perceptible increase in hazard to the patient is concerned.

2. Transfusion is the treatment par excellence in such cases, and in patients suffering from a wasting, debilitating type of disease it would seem to be the only type of treatment that produces any appreciable benefit, and even this procedure is not advisable in cases of inoperable malignant conditions in which radium offers no hope.

3. If sufficient time is available, very good results may be obtained in the simple anemias resulting from bleeding by the use of a nourishing amplified diet together with iron, either pills of ferrous carbonate or iron ammonium citrate.

4. The addition of liver to the diet probably has a slightly beneficial effect, but this is not sufficient to render its use essential, and it would probably be better to reserve the supply for the economic benefit of sufferers from pernicious anemia.

101 West Read Street.

# EPIDERMOID CYSTS OF THE SPLEEN

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DETROIT

Epidermoid cysts of the spleen have rarely been reported. A patient whom I have followed up for ten years after splenectomy had a megalosplenic cyst lined in part by a stratified epidermoid structure. This case will be discussed before a review of the cases so far described in the literature is presented.

## REPORT OF A CASE

*History.*—V. N., a white girl, aged 16, entered the Detroit Receiving Hospital on June 20, 1922, with the complaint of a gradual enlargement of the upper left part of the abdomen during the preceding two and one-half years. There had been an occasional slight local pain which was referred to the left shoulder. Once, about four months before, there was a sudden, sharp, severe pain in the region of the enlargement, accompanied by a marked degree of dyspnea. This was followed by a chill and a temperature of 104 F. The fever gradually subsided, and in a week the temperature was normal. There were no other acute symptoms. Shortness of breath on exertion had increased moderately. There had been no nausea or vomiting, no feeling of fulness after meals and no loss of appetite. There were no intestinal or urinary complaints. A loss of 7 pounds (3.2 Kg.) during the two months preceding admission to the hospital was attributed to a continuous round of good times.

The patient had had the usual children's diseases, with diphtheria, tonsillitis and smallpox. She had had an appendectomy and drainage of an appendiceal abscess five years before. Her menses began at the age of 11 and were never very regular. The last period was nearly two months before admission to the hospital. However, there had been no radical change in this function since the onset of the present complaint. A severe injury to her left side during childhood was not recalled until some days after splenectomy.

*Physical Examination.*—The general physical report, being irrelevant, will be omitted. The left costal margin flared markedly. In the upper left quadrant of the abdomen there was a mass which moved with respiration. It was smooth, soft and fluctuant, and was not tender to palpation. The rounded lower border curved from the tip of the left eleventh rib across the abdomen, just above the umbilicus, and disappeared behind the eighth left costal cartilage. No notch was felt.

*Laboratory Tests.*—Analysis of the blood showed: hemoglobin, 75 per cent; red cells, 4,010,000; white cells, 5,800. The differential white count showed: 67 per cent polymorphonuclears, 3 per cent large mononuclears, 26 per cent small mononuclears and 4 per cent eosinophil cells. The nonprotein nitrogen was 35 mg. per hundred cubic centimeters of blood. The blood sugar was 0.235 per cent. The Wassermann reaction of the blood was negative. The urine was normal.

*Roentgen Examination.*—The findings in the chest and the gastro-intestinal tract were reported by Dr. H. B. Doub as follows: The stomach and the lower portion of the esophagus are crowded over toward the right side beyond the midline.

The palpable mass in the left side of the abdomen causes a rounded incurving on the greater curvature of the stomach, but there is no involvement of the stomach. Most of the small bowel in the upper part of the abdomen seems to be present in the right side, but no organic pathologic condition is seen. The splenic flexure and transverse colon are displaced downward by the mass on the left side. No evidence of any involvement of the colon is seen. No pathology is seen in the chest with the exception of a slight elevation of the left diaphragm. The deformity seen seems to be due to pressure by the mass in the left upper quadrant of the abdomen, which appears to be the spleen.

*Operation and Course.*—On June 27, a vertical, upper, left, rectus, abdominal incision was made, and the mass described was found to be a splenic cyst. A trocar was inserted into this cyst, and 1,500 cc. of fluid was drained off. After freeing a few adhesions to the diaphragm and the abdominal wall about the costal margin and after multiple ligations of the pedicle, the spleen, together with the collapsed walls of the cyst, was removed. A small tip of the tail of the pancreas

Fig. 1.—A photograph of the exterior of the cyst. Note (*A*) splenic pedicle, (*B*) splenic border and (*C*) membranous wall of the cyst.

was accidently included in the pedicle ligatures. There was practically no bleeding, and after removal of the spleen no point of oozing was found. The liver, ovaries and other intra-abdominal organs appeared to be normal. The incision was closed in layers without drainage.

Convalescence was uneventful. Routine laboratory reports were all within range of normal, except that for several days there was a small amount of sugar in the urine. The blood sugar dropped from 0.235 to 0.153 per cent, but three days later had returned to normal. The patient was discharged from the hospital seventeen days after operation.

*Follow-Up Report.*—Thenceforth the patient was seen from time to time and had no important complaints or findings. In September, 1931, nine years after operation, she was more completely studied. Her healthy-appearing baby, normally born, after an uncomplicated pregnancy, was 25 months old at the time. The patient had had some vague upper abdominal pains. Physical examination showed a well healed left rectus incision, some tenderness over the gallbladder, barely

palpable inguinal glands and a slight enlargement of the thyroid. Examination of the blood showed no important changes from the findings before operation. The blood calcium was 12 mg. and the blood cholesterol 160 mg. per hundred cubic centimeters of blood. Roentgenograms of the gastro-intestinal tract revealed no pathologic changes; the gallbladder was visualized, and it emptied within normal limits.

*Pathologic Report.*—The specimen, in the preserved state, was ovoid and measured 22 by 17 by 12 cm. (fig. 1). The color was grayish blue. The blood vessels showed no gross changes. Most of the splenic tissue was flattened at the

Fig. 2.—Drawing of the interior of the cyst, showing trabeculae and recesses beneath the splenic remnant. *A* and *B* are small intrasplenic and subcapsular cysts.

hilum and over the upper pole of the cyst, and formed about one fifth of the external surface of the specimen. From a maximum thickness of 4 cm., it tapered gradually in all directions to become continuous with the fibrous membrane, which formed the lower part of the wall of the cyst. On the outer aspect of the lower membranous portion there was a scarred area 3 by 2 cm. in diameter. Some remains of adhesions were present on the upper surface of the splenic portion. Along the lower anterior margin of this upper portion several small clear cysts, averaging from 1 to 2 mm. in diameter, were seen projecting out under the splenic capsule. Section of the splenic portion revealed a few minute cysts in the pulp. The contents of these small cysts were serous. The interior of the lower portion

of the specimen was occupied by a single immense oval cyst cavity. The internal lining of the large cyst was perfectly smooth, except beneath the remnant of the spleen, where there were a richly developed trabecularism and ridge formation (fig. 2). These trabeculae appeared as interconnecting beams or arches, leaving both small and large recesses in between. This network was somewhat suggestive of the tendinous cords within the heart. The fluid content of the large cyst removed

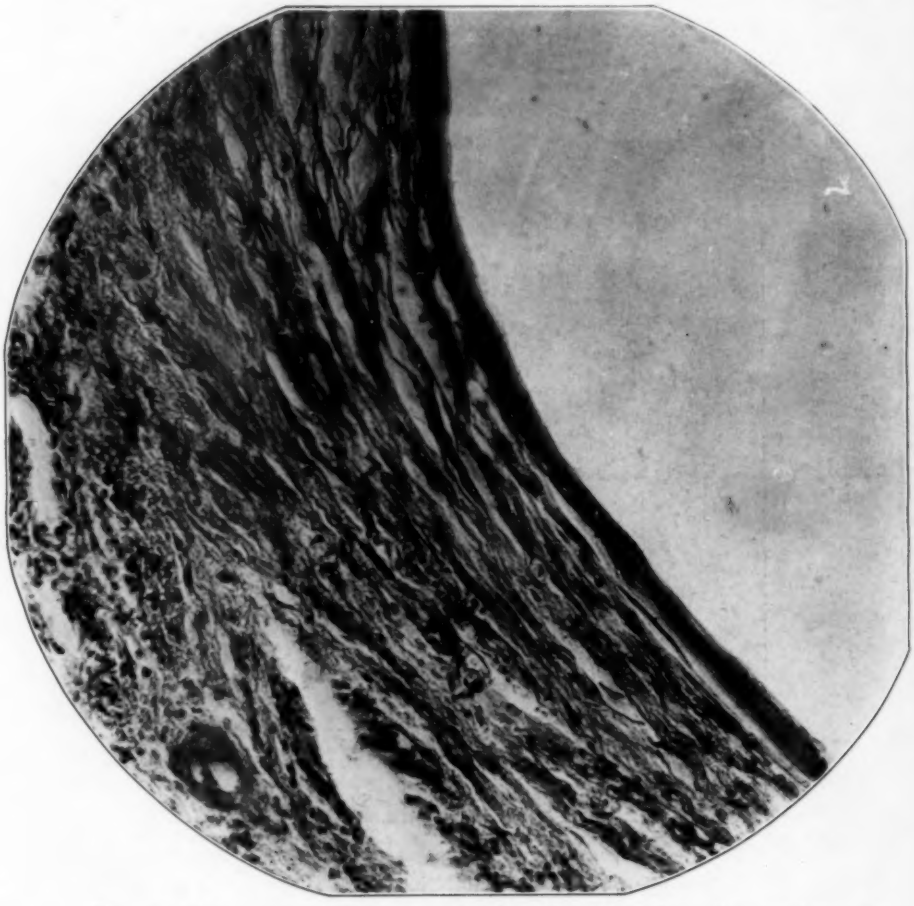

Fig. 3.—High power photomicrograph of section taken from the membranous portion of the wall of the cyst, showing no epithelial lining.

at operation amounted to 1,500 cc. This fluid was moderately thin, brownish and somewhat glistening, and contained fat, cholesterol and blood elements. No echinococci were present. A more complete chemical analysis was not made. Culture of the fluid evacuated resulted in no bacterial growth.

The original sections for microscopic examination immediately after splenectomy were taken only from the membranous portion of the wall of the cyst and showed fibrous connective tissue without any particular lining. It was nine years later,

during a follow-up examination, that a more complete pathologic examination was made, the result of which is most important in the present report. This microscopic examination was made of sections taken from additional areas of the wall of the cyst and from beneath the splenic remnant. Those taken from the lower portion of the membranous wall of the cyst showed, as originally, nothing of importance. The lining cells were mostly of the fibrous variety, poor in nuclei and sometimes hyalinized (fig. 3).

Fig. 4.—High power photomicrograph of a section taken from the membranous portion of the wall of the cyst. The arrow points toward an occasional flattened cell, forming the inner lining of the cyst.

Approaching the subsplenic area (fig. 4), a disconnected simple and gradually a stratified flat cellular lining was encountered next to the lumen of the cyst. In the depths of the niches and recesses this lining became from eight to ten layers thick (fig. 5). On the surface of the lumen there were several layers of flat or spindle-shaped cells, having flattened nuclei. The next three or four layers of cells were polyhedral, and the nuclei were more ovoid. The deepest cell layer was laid

down in a more perpendicular manner and had deep staining rounded nuclei. Under this lining was a loose connective tissue layer which had a different appearance from the connective tissue cells making up the trabecular framework. Definite cornification was not present. In no areas were sweat glands or hair follicles present. The few small cysts in the splenic parenchyma and those just beneath the peritoneum were lined by a more or less continuous layer of flat cells. Certain sections crossed the deep portions of the recesses in such a manner as to make

Fig. 5.—Low power photomicrograph taken from the splenic portion of the wall of the cyst. Note the invagination of the epithelial lining, which is of the stratified pavement type (indicated by arrow).

them appear as islands of many layered pavement cells deposited on a loose connective tissue base (fig. 6). A specimen taken from the splenic parenchyma showed some rather large lymph nodes, some hyaline degeneration and a definite increase in the connective tissue elements (fig. 7).

*Summary.*—In conclusion, it may be stated that this large cyst of the spleen had an inner lining of different degrees of stratification, varying from areas where

a lining was absent or was flat and single-layered to areas that were from five to ten layers thick. The thickest layering was found in the depths between the trabeculae, where it rested on a loose connective membrane. Although this stratified epithelium resembled the epidermis, it was unlike the latter because of the lack of hair follicles, sweat glands, papillary layer and cornification. The splenic remains were normal except for an increase in the connective tissue elements.

This case presents certain things of interest from the clinical, technical, follow-up and pathologic standpoints.

Fig. 6.—High power photomicrograph of the splenic portion of the wall of the cyst, showing a detailed structure of the epithelial lining. The island of stratified pavement epithelium is a cross-section of one of the recesses between the trabeculae. Note the lumen surrounded by many layered pavement cells on a deep staining germinal layer which rests on loose connective tissues (shown by arrow).

## CLINICAL ASPECTS

From the clinical standpoint, the splenic cyst occurred in a young girl having had slight menstrual irregularities and who also recalled having an injury to the left epigastric region. The relative frequency of splenic cysts in women during the menstrual life is supported by

reports from Hamilton and Boyer [1] (65 per cent) and others. Abdominal injury supposedly resulting in intrasplenic hemorrhagic cysts has often been reported in the literature. On the other hand, according to Frank's [2] statistics, only 22 per cent of seventy-two cases of large splenic cysts gave a history of previous abdominal trauma. Brandberg [3]

Fig. 7.—Low power photomicrograph of the splenic remnant, showing marked increase in connective tissue elements. Note (*A*) the large connective tissue trabecula.

remarked that "the injury, which need not be particularly severe, is often forgotten when the cysts begin to give symptoms." The pre-

1. Hamilton, C. S., and Boyer, E. H.: Hemorrhagic Cysts of the Spleen, Ann. Surg. **73**:58, 1921.

2. Frank, L. W.: Unilocular Cysts of the Spleen, Ann. Surg. **75**:360, 1927.

3. Brandberg, R.: Nonparasitic Cysts of the Spleen, Acta chir. Scandinav. **63**:346, 1928.

dominant symptoms were mainly mechanical, while the roentgenographic discovery of displaced gastro-intestinal viscera was the most valuable preoperative diagnostic aid. A preliminary aspiration of most of the fluid contents of the cyst rendered splenectomy easy to perform. Contrary to the usual belief, pregnancy may occur in a splenectomized woman, as brought out by the case reported, as well as by the recent article of Mussey and Burkley.[4] These investigators reported thirty-two pregnancies in a series of twenty-three women who previously had had their spleens removed.

## PATHOLOGIC ASPECTS

It is beyond the scope of this paper to discuss all types of splenic cysts. Suffice to say that they have been well covered in the papers of Fowler,[5] Howald,[6] Pool and Stillman,[7] Lubarsch [8] and others. They are usually classified as: (1) dermoid, (2) nonparasitic and (3) parasitic. Fowler [5] stated that there are two cases of dermoid cysts and ninety of large nonparasitic cysts recorded in the literature. That parasitic cysts are more common is indicated by his estimation of a possible total of one hundred and ninety-one cases reported up to 1894.

Morphologically, nonparasitic cysts can be divided into the large solitary and the small multiple varieties. Based on their possible origin, Fowler suggests that nonparasitic cysts of the spleen be classified as traumatic, inflammatory, degenerative, dilative and neoplastic. Under neoplastic cysts, which include lymphangiomas and hemangiomas, might also be included dermoid cysts, of which only two have been reported (Andral,[9] 1829, and Kumaris,[10] 1915).

To date, reports concerning cysts lined with stratified epidermoid cells are but three in number, so far as I have been able to ascertain. Because they have never been considered together before, I shall at this time briefly review the reports and findings.

1. Schneider [11] (1929) presented before the German Pathological Society a cystic spleen removed from a boy of 14 years. In an exten-

4. Mussey, R. D., and Burkley, G. G.: Pregnancy Following Splenectomy, M. Clin. North America **13**:1455, 1930.

5. Fowler, R. H.: Further Studies of Cysts of the Spleen, Ann. Surg. **80**:58, 1924.

6. Howald, R.: Pathogenese der grossen Milzcysten, Frankfurt. Ztschr. f. Path. **33**:349, 1926.

7. Pool, E. H., and Stillman, R. G.: Surgery of the Spleen, New York, D. Appleton and Company, 1923, p. 254.

8. Lubarsch, O., in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, p. 1.

9. Andral, G.: Précis d'anatomie pathologique, Paris, Gabon, 1829, p. 432.

10. Kumaris: Milzdermoid und Wandermilz, Arch. f. klin. Chir. **106**:699, 1915.

11. Schneider, P.: Eine splenomegalische Epidermoidzyste, Verhandl. d. deutsch. path. Gesellsch. **24**:280, 1929.

sive analysis of the same case, Dinand [12] (1930) wrote that during the discussion which followed Schneider's presentation, Lubarsch recalled an analogous observation that had not yet been published. In describing the lining wall of the cyst, Schneider observed:

> It shows an epithelial lining which at the areas of greatest pressure is uniformly reduced to a single layer of flat cells or is entirely lacking and then is replaced by a fatty granulation tissue. In the still intact areas of growth, however, in the recesses and niches, there is found a many layered pavement epithelium, from five to ten layers high, which sits directly on the splenic trabecular structure without any border or has only a loose skinlike connective tissue layer between it and the trabecular structure. Just occasionally, the epithelium still shows a trace of a germinal layer of dark cells, but for the most part, it consists of light, polyhedral cells with a distinct prickle cell layer; at the upper surface are found flattened cells without cornification. In spite of many examinations, no cutaneous glands or hair follicles could be found.

To explain its origin, Schneider believed that during the development of the spleen in the mesogastrium, some embryonic material lying in the celomic cavity, capable of forming epidermis, was enclosed in the splenic anlage. He denied the possibility of an origin from the spleen itself. He regarded his case as a true epidermoid cyst, and remarked that so far simple epidermoid cysts of the spleen seem not to have been previously reported. Dinand [12] (1930), in discussing the same specimen, assumed either an embryologic displacement or an autochthonous formation from the splenic tissue itself as an explanation of the tumor, and especially of its epithelial lining.

2. Pohle [13] (1929) reported a cystic spleen with similar microscopic findings removed from a 19 year old girl. In his microscopic report, he stated: "It is remarkable to find typical stratified pavement epithelium at one place or another, many times with clearly distinguished intercellular bridges, as the lining of the cyst. Two islands of pavement epithelium situated in a splenic tissue are especially to be noted. Hair follicles and cutaneous glands are not observed anywhere." He concluded that his specimen must most likely be regarded as a congenital dermoid cyst, although its development through metaplastic processes nevertheless appeared possible.

3. Santy [14] (1930), in reporting a splenic cyst removed from a boy of 15 years, described a more or less disconnected inner epithelial lining consisting of two or three layers of pavement epithelium. He noted a close resemblance to the transitional pavement cells of the

12. Dinand, F.: Riesige epitheliale Solitärcyste der Milz, Arch. f. klin. Chir. **158**:485, 1930.

13. Pohle, W.: Ueber Milzcysten, Deutsche Ztschr. f. Chir. **221**:211, 1929.

14. Santy, P.: Splénectomie pour un kyste vrai de la rate chez un enfant, Lyon chir. **27**:101, 1930.

wolffian bodies. The possible embryoplastic origin from a misplacement of a portion of the wolffian body was also considered by Dinand, who recalled the close position of the anlagen of the spleen and the generative organs in the early stages of embryologic development.

## COMMENT

In reviewing this group of three cases and my own case from the pathologic standpoint, one is struck by the uniformity of the structural findings. Macroscopically, in each there is found a large cyst of the spleen. The flattened splenic tissue forms a small portion of the wall of the cyst, the remainder being made up of a fibrous connective tissue capsule. The inner wall of the cyst beneath the remnant of the spleen presents numerous tendon-like ridges and trabeculae between which are found recesses and niches. Microscopically, the inner walls of these recesses adjacent to the spleen are lined by stratified, squamous, epidermoid tissue. Between this and the splenic trabecular structure is a loose connective tissue layer. This lining in the recesses resembles the skin, except that cornification, hair follicles, sweat glands and papillae are absent.

To explain the ontogenesis of these tumors, and especially of their epidermoid lining, one may resort to the theory either of embryologic displacement or of autochthonous formation.

*Embryologic Displacement.*—It is possible to have an ectodermal metaplasia in the splenic anlagen. This island of ectodermal tissue may eventually be causative in the formation of a tumor mass and cyst. However, this possibility is not probable in these cases because of the lack of associated structures so commonly seen when an ectodermal metaplasia occurs.

It is also possible that this lining may have its origin in the kidney anlagen capable of producing transitional epithelium. The latter, under certain circumstances, may simulate the stratified squamous epithelium of the skin, including cornification.

*Autochthonous Formation.*—According to this theory, it may be postulated that mesoderm has the ability to form the products of any of the other two primary germinal layers. Thus, for some unexplained reason, the cyst lining may be of the squamous stratified type on the basis of a mesodermal origin. This theory is particularly supported by the work of Fischel.[15] He stated that "the ectoderm and entoderm furnish the organs in the development of which they are concerned, with the epithelial portion only. They, themselves, are unable (with the possible exception of the lens and vitreous humor)

15. Fischel, A.: Lehrbuch der Entwicklung des Menschen, Berlin, Julius Springer, 1929.

to develop an organ in its entirety. On the other hand, an organ may consist entirely of mesodermal tissue, for the mesoderm is able to supply the epithelial element as well as the connective tissue." H. Müller,[16] in his article on the histologic agreement between epithelial degeneration and cancer growth (also reported by Dinand), cited examples of the apparent formation of epidermoid tissue from a germinal tissue layer other than the ectoderm, and concluded that epithelial formation in pathologic processes is not bound by the rule of specificity. Müller presented a photomicrograph of the inner lining of an olecranon bursa which looks much like the photomicrograph seen in Pohle's report and that taken in my case of splenic cyst. This shows many layers of stratified pavement epithelioid cells, a germinal-appearing layer and an underlying loose connective tissue layer which simulates the structure of the epidermis. Here, too, cornification and cutaneous glands are lacking. From these statements, it seems that the development of epidermoid tissue from mesoderm may occur.

SUMMARY

1. Epidermoid cysts of the spleen have rarely been described. Only four instances, including the case here presented, plus another unpublished case recalled by Lubarsch, have been noted.

2. So far, all epidermoid cysts of the spleen have been described in young people. Sex seems to play no especial rôle, as two occurred in boys and two in girls.

3. Complete and repeated microscopic examinations of all splenic cysts may add to the number of these epidermoid cysts.

4. Tumor and distress in the splenic region coupled with elimination of other tumors by various clinical methods, especially radioscopic studies, facilitate the correct diagnosis of large splenic cysts.

5. Splenectomy, the most satisfactory treatment in large unilocular cysts, is facilitated by a premliminary evacuation of the contents of the cyst, providing the presence of parasites has been ruled out.

6. A ten year follow-up in the case herewith presented shows no apparent morbidity after splenectomy. One case of normal gestation in a splenectomized woman is added to those previously collected.

16. Müller, H.: Die histologische Uebereinstimmung zwischen Epithelregenration und Krebsbildung, Ztschr. f. Krebsforsch. **28**:383, 1929.

# INVAGINATION OF THE APPENDICAL MUCOSA PRODUCING SYMPTOMS RESEMBLING APPENDICITIS

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In one week in February, 1931, in the course of routine work, two appendixes were sectioned which showed unusual lesions, and these lesions could be linked up in an interesting way with the clinical data. Therefore, I am presenting the cases in detail.

## REPORT OF CASES

CASE 1.—Mrs. A. S., aged 20, who was first seen in the University of Chicago Clinics, on Dec. 30, 1930, complained that since a delivery five months previously, she had had pain in the lower part of the abdomen and the back almost constantly, accompanied by weakness and apparently unrelated to meals or activity. There was some tenderness low in the midline and in the lower quadrants of the abdomen. On pelvic examination the adnexa seemed to be slightly enlarged and tender. The Wassermann and Kahn tests were negative. The white cells numbered 6,200; the urine was normal. Conservative treatment was advised.

When the patient was seen on Jan. 13, 1931, she had made no improvement, and the masses in the adnexa uteri seemed larger and more tender. She was accordingly admitted to the hospital for further observation on January 29. At that time, there was a white cell count of 8,600, a faint trace of albumin in an alkaline urine and a sedimentation time of 7 mm. per hour. The temperature was as high as 99.4 F. on several occasions. On February 4, a supracervical hysterectomy with a bilateral salpingo-oophorectomy was performed by Dr. M. E. Davis. The distal end of the appendix was injected and slightly bulbous, so an appendectomy was also performed. There was a febrile course, and the patient was discharged on February 18, with a small elevation of daily temperature (from 99.2 to 99.8 F.). When the patient was seen on May 18, for the last time, she had made an excellent recovery and seemed quite normal.

The gross operative specimen showed nearly normal tubes and ovaries, with a slightly thickened appendix. Microscopically, the tubes and ovaries were also almost normal, but the appendix showed unexpected changes. Inside the usual muscular coat was a thin layer of condensed and atrophic lymphoid tissue which, in a few places, showed the typically glandular character of mucosa and submucosa. Intimately apposed to, and within this layer, was an exactly similar one, but the two layers were everywhere distinct and in some places definitely separated. The line of demarcation between them was continuous and regular throughout the whole circumference of the sections studied. Inside the inner glandular layer and outside the outer layer was a loose structure composed of strands of muscularis. The mucosa and submucosa at the center of the section were not involved.

The whole picture suggested an invagination of the mucosa and submucosa of considerable duration sufficiently impacted to produce a pressure atrophy of the surrounding mucosa and submucosa.

The specimen is shown in figure 1.

CASE 2.—Miss N. L., aged 33, was admitted to the hospital on Jan. 2, 1931, on the service of Dr. Walter Palmer. She had been well until four weeks previously, when she began to have sharp pains in the epigastrium and the right upper quadrant of the abdomen, with a dull aching distress in the left lower quadrant and left groin. Her period began three days after the pain, one week prematurely.

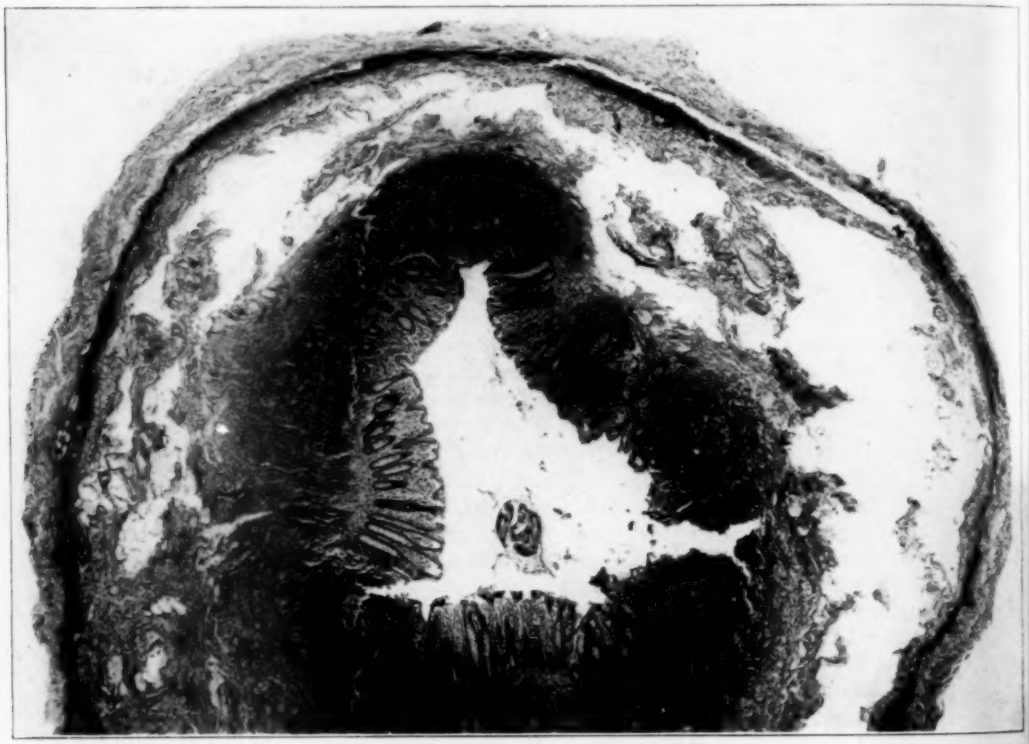

Fig. 1.—Low power view of appendix (case 1).

The pain in the left lower quadrant soon subsided, and was followed by pain in the right lower quadrant, which was dull and steady, but became sharp on deep respiration, slight movement or jarring of the bed, and radiated to the right upper quadrant and epigastrium. This was constant for three weeks. She vomited once in the early part of her illness. The distress had no relation to food or bowel movements. At times the weight of the bed clothes was painful. When the patient was admitted she had residual soreness in the lower part of the abdomen, especially in the right lower quadrant. Examination revealed tenderness in the right lower quadrant, especially over McBurney's point, with slight spasm of the right rectus. Pelvic examination showed retroversion of the uterus and resistance in the right

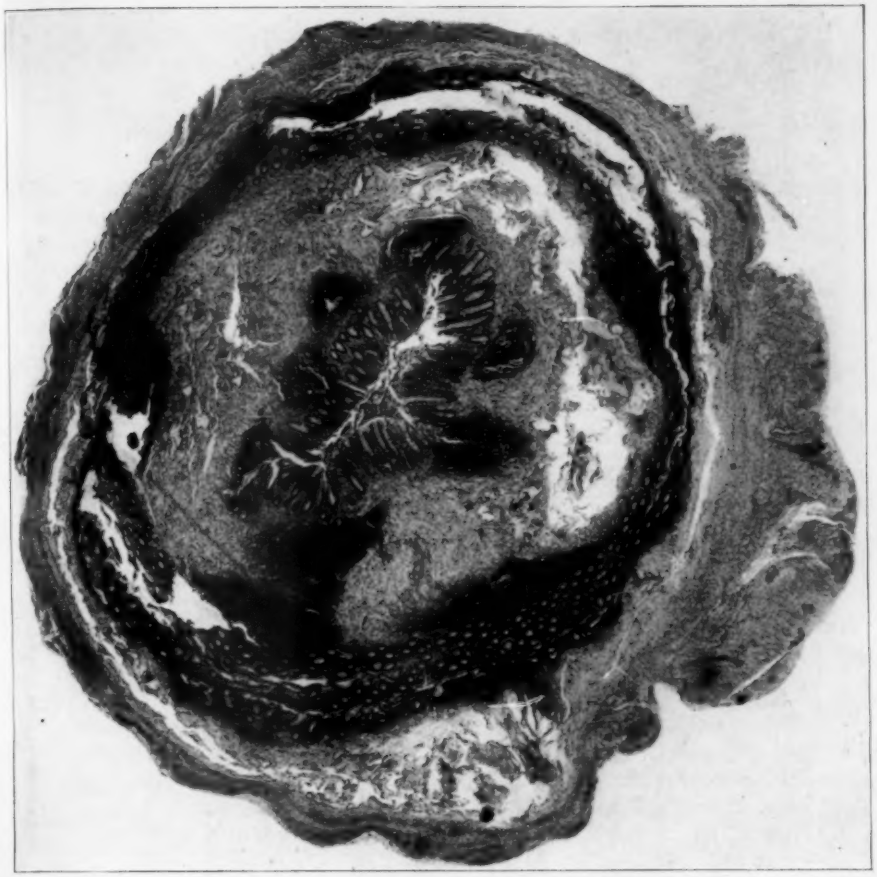

Fig. 2.—Low power view of appendix (case 2).

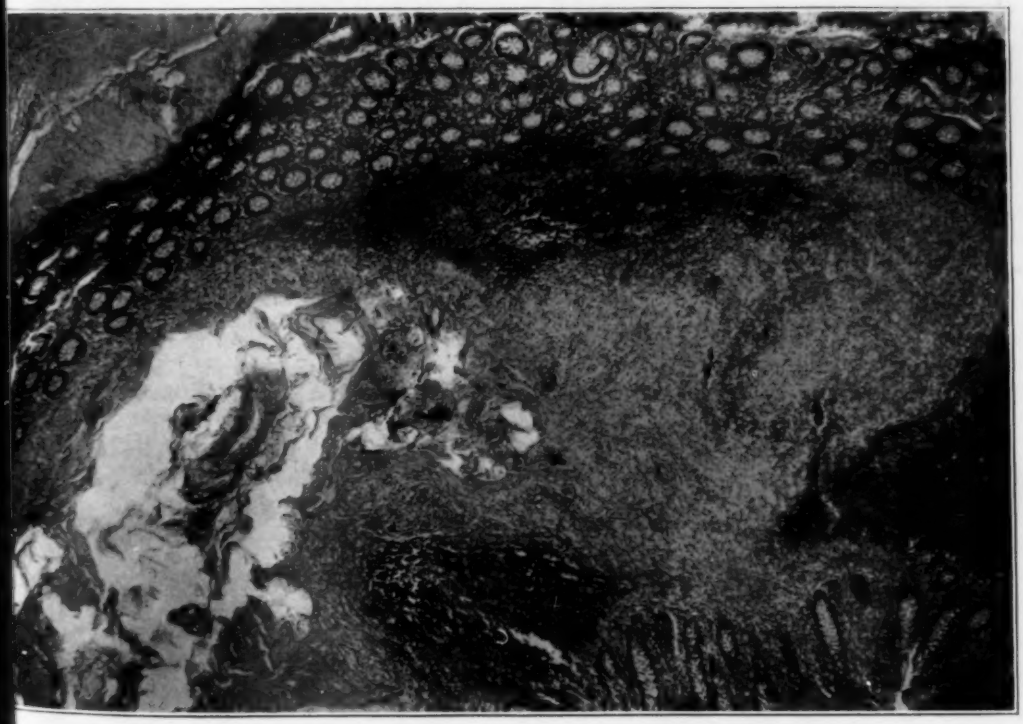

Fig. 3.—High power view of appendix (case 2) showing clearly the two layers of mucosa approximated by the invagination.

adnexa, but the point of maximal abdominal tenderness was definitely above the tubes. There was a leukocyte count of 12,000, of which 64 per cent were polymorphonuclears. The urine was concentrated. Wassermann and Kahn tests were negative. The previous history of disease was unimportant. There had been no previous injuries or operations. The patient refused operation. On January 5, she was discharged as having subsiding acute appendicitis.

The patient had severe epigastric pain on January 18, from 10 p. m. to 1 a. m., without chills or vomiting. The next day there was pain in the lower part of the abdomen, especially in the right lower quadrant, which subsided gradually in the next day or so. However, at 3 a. m. on January 21, the patient was awakened by a sharp stabbing epigastric pain which doubled her up. She vomited an hour later. The pain was somewhat relieved by 6 a. m., but a steady ache remained in

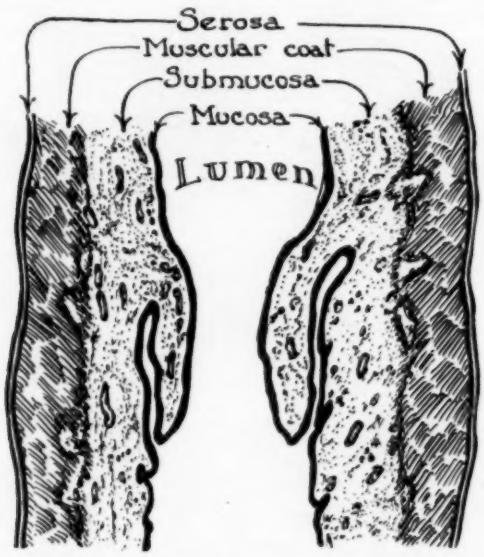


Fig. 4.—Diagrammatic representation of the phenomenon of invagination of the appendical mucosa.

the right lower quadrant. Another brief epigastric attack occurred at 9 a. m. The patient was readmitted to the hospital, and was found to have no fever or abdominal rigidity, but some tenderness at McBurney's point, with definite rebound tenderness. The symptoms rapidly subsided and again a diagnosis of an atypical subsiding acute appendicitis was made. Pelvic examination on January 26 showed the left ovary slightly adherent and enlarged and a right ovarian mass that was tender and adherent. On February 5, these masses had enlarged. At the time of the second admission the white cell count was 17,000, of which 45 per cent were polymorphonuclears and 45 per cent lymphocytes. The urine was normal. On February 6, the sedimentation time was 33 mm. per hour. The following day Dr. F. L. Adair performed a bilateral salpingectomy and removed the appendix. There were filmy adhesions about the tubes and evidences of salpingitis, but the appendix seemed normal. There was an easy postoperative course, and when seen on March 12, the patient was found to be in good health and free from symptoms.

Examination of the operative specimen showed characteristic inflamed tubes slightly thickened and congested. The appendix was slightly thickened, and there were recent fibrinous adhesions about it. Microscopically, there was a typical subacute salpingitis and an interesting appendical condition essentially like that in case 1. However, there was no such definite atrophy of the mucosa and submucosa of the outer ring or of the apposed portions of the invaginated mucosa (figs. 2 and 3).

Figure 4 represents diagrammatically the lesion characteristic of these two cases, as seen on sagittal section taken through the appendix.

## COMMENT

The literature contains many reports of complete or partial intussusception of the appendix. In 1922, Szenes [1] collected the literature up to that time. He found only one case of intussusception of the appendix into itself in which there was no cecal involvement as well, viz., the case of Kuss and Guimbellot. However, he cited Rolleston's [2] case and Schmidt's two cases, in all three of which there was a pseudo-invagination and incomplete involvement of the appendix. In a later review, Huddy [3] remarked that Szenes apparently overlooked the cases of Treves,[4] Johnson,[5] MacClennan's [6] two cases, and an unpublished specimen in the museum of the Royal College of Surgeons obtained by H. B. Robinson.[7] Szenes also overlooked several cases cited by Battle and Corner [8] in their good review of 1911, namely, Bishop,[9] Furniss [10] and Grisel.[11] Huddy adds to the list of the cases published a number appearing since Szenes' paper, namely, those of Evans,[12] Hipsley,[13] Brin and Fruchaud-Brin,[14] Huese,[15] Trince,[16] McIntosh,[17] and

1. Szenes, A.: Arch. f. klin. Chir. **119**:88, 1922.
2. Rolleston, H.: Edinburgh M. J. **4**:21, 1898.
3. Huddy, G. P. B.: Brit. J. Surg. **14**:580, 1927.
4. Treves, Frederick: Intestinal Obstruction, Philadelphia, H. C. Lea, 1884, p. 172.
5. Johnson, G.: Brit. J. Surg. **3**:564, 1916.
6. MacClennan: Clin. J. **48**:78, 1919.
7. Robinson, H. B., cited in Battle, W. H., and Corner, E. M.: Surgery of Diseases of the Appendix, London, A. Constable & Company, 1910, p. 193.
8. Battle and Corner (footnote 7).
9. Bishop: Chironian **10**:81, 1902, cited by Battle and Corner.
10. Furniss: Am. J. Obst. **58**:307, 1908.
11. Grisel, P.: Maladies du tube digestif, Paris, 1908, vol. 2, p. 333; cited by Battle and Corner.
12. Evans, A.: Brit. J. Surg. **9**:565 (April) 1922.
13. Hipsley, P. L.: M. J. Australia **2**:65 (July 15) 1922.
14. Brin and Fruchaud-Brin: Bull. et mém. Soc. anat. de Paris **93**:243, 1923.
15. Huese, J. F. O.: Nederl. tijdschr. v. geneesk. **1**:2393, 1923; cited by Huddy (footnote 3).
16. Trince: Riv. di clin. pediat. **21**:10, 1923; cited by Huddy.
17. McIntosh, R. D.: M. J. Australia **1**:216 (Feb. 25) 1922.

doCouto.[18] I should like to add those of Bobrik,[19] Whitrow,[20] Horn,[21] Hamilton,[22] MacDermott,[23] and the unpublished cases of Myles and O'Connor which MacDermott mentioned to complete the list of publications to date.

However, no case so far reported seems to present quite the same conditions as those found in the two cases reported in this paper. It is true that Rolleston noted that in his case the mucosa alone was involved in the intussusceptum, and that except for the dense adhesions, from the outside nothing abnormal would be suspected. The lesion was discovered only at autopsy when the cecum was opened; the invaginated portion was only about ½ inch long (12 mm.). In Schmidt's two cases there were appendical cysts, and the appendix seemed normal externally. Watson's [24] case was very similar to Rolleston's, and led to the formation of a long intussusceptum.

Appendical valves are not described in the literature, so far as I know. The picture presented by our specimens would not coincide even with such an explanation, however. It is true that the segment of appendix containing the invaginated mucosa was only a few millimeters long, as was found by taking serial sections of the involved portion. Intestinal valves rarely extend around the whole periphery of the bowel, but tend to be crescentic. The sections of our specimens all showed, however, a symmetrical relation of the containing and contained portions of the appendix, and Dr. F. L. Adair commented on the importance of this feature in diagnosis. Prof. H. G. Wells remarked on the pressure atrophy of the mucosa and submucosa of the outer ring, which was seen best in case 1, in which the impression of an invaginated portion sufficiently large to exert considerable pressure for some time was obtained. It was suggested by Dr. R. S. Jason and later by Prof. H. G. Wells that this was a sort of intussusception of the appendical mucosa. The slides have been studied by Dr. F. L. Adair, Dr. R. S. Jason and Dr. H. G. Wells, and all agreed on the diagnosis.

Christeller and Mayer (see Rössle) and Rössle [25] have observed a few cases in which portions of mucosa had grown down into the muscularis along fistulous tracts or to line abscesses in the wall. Rössle

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18. doCouto, J.-E.: Etude sur l'invagination de l'appendice, Thèse de Paris, 1925; cited by Huddy.

19. Bobrik, N.: Zentralbl. f. Chir. **41**:518 (March 2) 1929.

20. Whitrow, F.: Brit. M. J. **2**:181 (Aug. 2) 1930.

21. Horn, H. W.: Ann. Surg. **81**:1002 (May) 1925.

22. Hamilton, T.: M. J. Australia **1**:408 (April 4) 1931.

23. MacDermott, E. N.: Brit. M. J. **1**:793 (May 9) 1931.

24. Watson, J. H.: Lancet **2**:942, 1911.

25. Rössle, R.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **42**:143, 1930.

shows a fine picture of such a specimen. A moment's consideration will show how different is the picture presented by the appendixes in the present cases.

It is to be noted that the muscularis in the deep submucosa in both these appendixes was very loose and almost fragmented for a considerable distance on each side beyond the actual site of the telescoping phenomenon. This allowed easy motion of the mucous layer on the adjacent wall. No inflammatory process ensued in these appendixes. The filmy adhesions seen in case 2 were entirely of pelvic origin. Microscopic examination did not reveal periappendicitis or appendicitis. The symptoms developed in each case from a lesion that was entirely mechanical. The observations were quite accidental. Most normal-appearing appendixes are casually treated everywhere, and one cross-section is usually thought sufficient to demonstrate the presence or absence of inflammatory involvement. However, the importance of longitudinal sections or at least numerous cross-sections of every appendix is clearly demonstrated by the aforementioned observations.

The symptoms in case 2 were definitely appendical, of four weeks' duration, and were characterized by at least two exacerbations sufficiently marked to warrant admission to the hospital for appendicitis. The classic phenomena were present to some degree, but there was no fever. The vomiting was slight; the leukocytosis, especially of polymorphonuclears, was slight, and the symptoms were unduly prolonged at a subacute level. There was no marked rigidity and no modification of bowel or urinary habit. The whole picture in this case, of course, was complicated by the adjacent active salpingitis, but I think that the major portion of the symptomatology was due to appendical factors. In case 1 the patient showed abdominal distress and pelvic signs of a more indefinite character, but the only significant finding was the appendical one, and most of the patient's symptoms must be ascribed to the appendix.

The occurrence of repeated appendical attacks, none of which is definitely an "acute appendicitis," with its characteristic low fever, vomiting, leukocytosis, temporary constipation, or urinary frequency, marked right rectus rigidity and localized tenderness should suggest the possibility of an appendical lesion of a type not hitherto suspected. MacDermott noted that slight intussusceptions may produce vomiting late or early, with no rise in temperature, pulse or increase in abdominal rigidity until the appendix becomes inflamed. Many a surgeon has felt slightly ashamed to operate for "appendicitis" of this type, even if it produced prolonged and marked discomfort such as was found in our two cases; he has been more regretful when no gross or microscopic changes in the suspected organ were visible. In such cases more cross-sections or longitudinal sections might have revealed just such a lesion

as I am discussing. MacDermott wonders, "if recurrent intussusception, spontaneously reduced, may not frequently be the real lesion in many cases which, though presenting no obvious lesions at laparotomy, are relieved of symptoms by appendectomy." He cited Alvarez' films of intestinal movements which show intussusceptions occurring and reducing themselves spontaneously. He mentioned an unpublished observation of Myles of such an invagination of the appendix into the cecum, occurring spontaneously and reducing itself with regular rhythm in a patient on whom he was operating for cecal hernia. He ascribes the beneficial effects of atropine in some cases of "chronic appendicitis" to similar processes.

As regards etiology, it is now generally accepted that the appendix is a mobile organ with peristaltic activity. Movement of the internal layers may occur apparently even when the serous coat is fixed by adhesions, as in Rolleston's case and our case 2. Bohême and Reny [26] remarked that at the appendix the colon's antiperistalsis meets the ileal and appendicular peristalsis so that telescoping at this site readily develops. At the meeting place of these waves of peristalsis and antiperistalsis adjacent portions of virtually the same organ are synchronously relaxed and contracted, a situation which is ideal for telescoping phenomena. If there is a mild inflammation adjacent to the appendix it is probably stimulated to increased activity. It is well known that the ileocecal-appendicular region is the focus from which most intussusceptions of the bowel begin. If the distal end of the appendix is adherent, the waves from the bowel running into it tend to force it into the adjacent distensible cecal cavity or into its own relatively large base. The factors that influence intussusception of the organ, as a whole, also have the same effect on its component layers, especially when those layers are loosely bound together, as in the cases which I am reporting. There is no good reason why the factors necessary to produce such lesions should not often arise, and I suspect that they are not uncommon.[27]

26. Bohême, P., and Reny, P.: Rev. de chir. **47**:287, 1929.

27. Dr. F. L. Adair and Dr. M. E. Davis gave me permission to publish the two cases described.

# OSTEOMYELITIS OF THE SKULL

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## INTRODUCTION

The present communication is concerned with osteomyelitis of the flat and irregular bones of the skull exclusive of the maxilla. The principles of the pathogenesis of acute osteomyelitis in general will be incorporated in this paper as they apply to osteomyelitis of the skull, and any differences from the usual manifestations found in the long or other irregular bones of the body will be found to occur as a result of the essential structure of the cranial bones. Any extraordinary phenomena associated with osteomyelitis of the skull that occur in a large clinical group result from its origin in the neighboring nasal accessory sinuses or in the otologic apparatus, and are associated mainly with the development of intracranial secondary complications which commonly dominate the clinical picture.

In this communication I shall consider only those cases of acute osteomyelitis of the skull that are caused by the common pyogenic organisms—staphylococci, streptococci, pneumococci, etc. I shall not include any cases due to infection by the tubercle bacillus, Spirochaeta pallida or by Actinomyces.

Cases of acute osteomyelitis of the skull frequently last a long time and assume the characteristics of a chronic infection; such cases are included, as one should consider them to be long drawn out cases of acute osteomyelitis. No other variety of chronic pathologic process of the bones of the skull is, however, included in this discussion; neither are the forms of necrosis of the skull due to phosphorus or other similar forms of poisoning, nor the group of peculiar cases marked pathologically by various forms of hypertrophic osteitis included. Cases of acute and chronic bone change associated with certain forms of essential blood disease are, of course, completely separated from the subject.

## HISTORICAL

Although osteomyelitis of the skull undoubtedly must have occurred frequently prior to the eighteenth century as a consequence of civil and military injuries about the head, involving the skull, the association of the injury and the consequent clinical manifestations with infection of the bone tissue of the skull was not suspected or recognized until long

From the Mount Sinai Hospital.

after knowledge was prevalent concerning similar associations in the long bones. The skull conditions were first described by Pott [1] in 1768 under the name of bone contusion. He believed that these lesions were always caused only by contusion. He assumed that in every severe contusion detachment of the dura mater is caused by an extradural hematoma; that the hematoma irritates the dura, and that the irritation increases and causes suppurative inflammation. In 1859, Chassignac [2] suspected that the condition was a true bone disease, but this remained only a theory until it was proved by Lannelongue [3] in 1879 that cranial para-osseous abscesses were due to disease of the bone itself. It was then still a hundred years before the real nature of the disease was known, and the route of infection was not discovered until even later than that. In 1882, Fischer [4] wrote of apparently spontaneous inflammation of the skull that it was probably caused by progressive suppuration in the neighboring tissues. In 1889, cases of cranial osteomyelitis having an origin in the nasal accessory sinuses were described by Luc [5] and Tilley.[6] Later cases were reported in which there was an otologic origin. Finally, as bacteriologic knowledge increased, it began to be recognized that osteomyelitis of the skull could also be hematogenous or metastatic, and the first mention of this etiologic relationship is made by von Bergmann [7] in his "Handbook of Practical Surgery" in 1900.

## FREQUENCY

In the modern period, and especially in the antiseptic and aseptic periods, cases of osteomyelitis of the skull following injury have become scarcer and scarcer, so that now it would be difficult, I imagine, for any one to gather together a hundred cases of traumatic osteomyelitis of the skull from his own experience, as Fischer did in 1882. On the other hand, with increasing knowledge, cases due to other causes, especially to nasal accessory sinus disease, have seemingly increased in number

1. Pott, P.: Observations on the Nature and Consequences of Those Injuries to Which the Head is Liable from External Violence, London, 1768.

2. Chassaignac (1859), quoted by Kallenbach: Beitr. z. klin. Chir. **128**:725, 1923.

3. Lannelongue, O.-M.: De l'ostéomyélitis aigue pendant la croissance, Paris, Asselin & Cie, 1879.

4. Fischer, H.: Deutsche Ztschr. f. Chir. **56**:100, 1900.

5. Luc: (*a*) Arch. de laryng. et rhinol. **12**:280, 1899; (*b*) J. Laryng. **14**:473, 1899; (*c*) Brit. M. J. **2**:993, 1899; (*d*) Ann. d. mal. de l'oreille, du larynx **28**:497 (Dec.) 1902.

6. Tilley, H.: Lancet, 1900, vol. 2; Tr. Lon. Laryng. Soc., March, 1904; Brit. M. J. **2**:7, 1917; J. Laryng. & Otol. **38**:78 (Feb.) 1923.

7. von Bergmann, A.: Handbuch der praktische Chirurgie, 1879; St. Peters. med. Wchnschr. **37**:38 and 389, 1884.

because the medical profession has learned to look for them and to recognize the etiologic relationship, and because attention is forcibly called to the lesion by the dramatically dominating secondary intracranial complications which take place.

One reason why nontraumatic forms of osteomyilitis of the skull were not recognized for such a long time is that they are so rare. Scheinziss [8] found that among 1,782 cases of osteomyelitis of the long and flat bones there were only ten of osteomyelitis of the skull; in Kiel there were four cases among 400, and in Kallenbach's [9] clinic, three among 620. According to Trendel,[10] only five cases have been seen in the Tübingen clinic in fifty years; in Kiel four cases have been seen in twelve years, and in Poppert's clinic in Giesen, three cases in fourteen years.

According to the records at Mount Sinai Hospital for the period from 1924 to 1931, there were 331 cases of acute osteomyelitis of all the bones of the body; among these there are records of seventeen cases of osteomyelitis of the skull—a percentage of 5.

In my own experience I have seen osteomyelitis of the skull as a hematogenous infection in one case, as an operative infection in one case, as a complication of nasal accessory sinus disease in two cases, and several traumatic cases—all of this in a space of twenty years. I believe this to be an average experience for a general surgeon.

According to Trendel,[10] who collated the statistics of Haaga [11] and Fröhner,[12] osteomyelitis in the flat bones occurs in the relationship of 1:6.6 to osteomyelitis in the long bones, and osteomyelitis of the skull occurs in about 3 per cent of the cases in the flat bones.

Taking the matter all in all, the number of cases of cranial osteomyelitis that are encountered at the present time in hospital and private practice are small and, possibly, will continue to grow smaller owing to greater knowledge of prophylaxis, especially in the care of the provocative origins in the nasal accessory sinuses and in the otologic apparatus.

## CRANIAL AREAS INVOLVED

The commonest location for the development of an osteomyelitis of the skull is the frontal and the parietotemporal regions. This is in correspondence with the common locations for the reception of head injuries, and because of the close contiguity to the frontal and other nasal accessory sinuses and to the auditory apparatus—the commonest sources of an extension form of osteomyelitis of the skull.

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8. Scheinziss, M. W., quoted by Kallenbach (footnote 9).
9. Kallenbach: Beitr. z. klin. Chir. **128**:725, 1923.
10. Trendel: Beitr. z. klin. Chir. **41**:607, 1904.
11. Haaga, P.: Beitr. z. klin. Chir. **5**:49, 1889-1890.
12. Fröhner, E.: Beitr. z. klin. Chir. **5**:79, 1889-1890.

In the cases at Mount Sinai Hospital the areas in which the osteomyelitis was distributed were as follows:

| | |
|---|---|
| Frontal bone | 6 cases |
| Frontal and parietal bones | 2 cases |
| Frontal and ethmoid bones | 2 cases |
| Temporal bone | 1 case |
| Temporal bone and zygoma | 1 case |
| Parietal bone | 1 case |
| Sphenoid bone | 3 cases |
| Sphenoid and ethmoid bones | 1 case |
| Petrous pyramid | 1 case |
| Zygoma | 1 case |

In Kallenbach's[9] series, the distribution was as follows:

| | |
|---|---|
| Frontal bone | 15 times |
| Frontal and parietal | 1 time |
| Temporal | 8 times |
| Parietal | 5 times |
| Occipital | 3 times |
| Sphenoid | |
| Frontal and temporal | 2 times |
| Frontal, temporal, parietal and occipital | 1 time |

## AGE

In consequence of the protean character of the causative origins of cases of osteomyelitis of the skull, the prevalent ages at which the cases seem to develop are in conformity with the ages for which these origins, trauma, nasal accessory sinus disease, etc., seem to have some special predilection. Traumatic cases are likely to occur at any time; extension cases, especially those of nasal sinus origin, are also likely to occur at any age, but develop usually in young or middle adult life; hematogenous cases follow the prevalence of these acute general infections with localizations in the bones and are apt to occur in childhood, at puberty or young adolescence. In the cases at Mount Sinai Hospital the age distribution was as follows:

| | |
|---|---|
| Up to 10 years | 5 cases |
| 11 to 20 years | 4 cases |
| 21 to 30 years | 1 case |
| 31 to 40 years | 1 case |
| 41 to 50 years | 5 cases |
| 51 to 60 years | 2 cases |
| 60 to 70 years | 1 case |

## PATHOLOGIC PROCESS IN OSTEOMYELITIS OF THE SKULL

*Gross Pathology.*—Mild cases affecting the external table of the skull correspond in their pathologic process to osteomyelitis of the long

bones limited to a relatively small area of the cortex. The circulation becomes shut off from a number of vessels in the external table and, depending on their number and on the extent of collateral circulation, a segment of bone is sequestrated and discarded. The sequestrated parts take the form of small flakes of bones, or thin segments of irregular shape. The suppuration that accompanies this gathers between the outer table and the pericranium and corresponds to a subperiosteal abscess of the long bones.

Mild cases affecting the internal table correspond in their particulars to those of the external table.

In more severe cases of osteomyelitis of the skull involving both the external and internal tables of the skull, and in the diffuse and in the spreading varieties, the pathologic process is more extensive, and a dominant place is taken by the diploic network of veins.[13] The description that follows applies generally to all types of osteomyelitis of the skull without reference to the etiologic cause or condition; it is, however, particularly applicable to cases that result from disease in the nasal accessory sinuses. The pathologic anatomic appearances of the lesions vary with the stage of the disease. In the early stages, the bone presents no abnormalities evident to the naked eye, although during life the diploe might perhaps show some congestion. In the next stage, the diploe on section is seen to be markedly hyperemic and to be interspersed here and there with drops of pus. This is followed by the conversion of the medullary tissue of the diploe into granulation tissue bathed in pus, which, on section of the bone, exudes copiously from the cut surfaces. Thrombosed veins may be seen occupying the diploe. In the third stage, the purulent secretion, finding its way to the outer and inner surfaces of the bony cranium by the vascular channels or through minute openings formed by the resorption of bone tissue, collects to form abscesses between the bone and the pericranium on the one hand, and between the bone and the dura on the other—the para-osseous abscesses.

In the external variety of abscesses, the pericranium, raised off the surface by the accumulation, quickly undergoes dissolution, so that the collection of pus comes to lie in the subcutaneous tissues of the scalp. No delimiting abscess wall is formed, but the pericranial abscesses are, nevertheless, when they are multiple, quite discrete and separate from each other. These are the doughy or puffy swellings of the scalp, which form a striking clinical feature of the disease.

The dura shows little or no tendency to break down for considerable periods of time. Larger and smaller collections of pus gather in the extradural space which, when sufficiently large, may give rise to com-

13. The anatomy of the diploic veins is described subsequently. See section on "Pathogenesis."

pression of the intracranial contents. The bony (external) wall of the abscess remains bare, but the dural (internal) surface becomes covered with shaggy granulations. Fine adhesions are usually demonstrable between the deep surface of the dura and the underlying arachnoid.

The fourth stage of the lesion is marked by more or less widespread destruction of the tables of the skull, the external usually giving way before the harder vitreous. By this time more or less extensive areas

Fig. 1.—Low power picture of a section of a skull the seat of an osteomyelitis of the diffuse type, showing the dead bone and the suppurating diploic spaces. (Figures 1, 2 and 3, courtesy of Dr. Klemperer.)

have undergone necrosis. Sequestration occurs either in large masses, sometimes of characteristic shape, or in small flaky segments. An eroded or wormeaten appearance of the outer table of the skull has given rise to such descriptive terms as "lace-work" (Tilley [6]), or as if it had been "corroded with acid" (Luc [5]).

During the active stages of the development of an osteomyelitis of the skull of this type, new formation of bone, which occurs with such

rapidity and exuberance in osteomyelitis of the long bones, either does not appear at all, or is scarcely perceptible. On microscopic examination, some little attempt at regeneration may be visible, but it is entirely overshadowed by the processes of destruction. Indeed, in this respect, as in many others, the reactive efforts of the tissues seem to be feeble and incompetent. In favorable cases, in which healing and cicatrization become definitely established, however, the gaps made in the skull by the spontaneous, or operatively produced, loss of tissue are almost filled up again by the formation of new bone.

Fig. 2.—Higher power picture of one of the diploic spaces, showing the dilated diploic veins and the suppurative inflammation that is present. Osteoclastic destruction of the bone is visible at the periphery of the space; × 140.

*Microscopic Pathology.*—Microscopically, early specimens show that the first changes consist in an invasion of the bone spaces by micro-organisms, with round cell infiltration of the medullary spaces, the walls of which, at this period, are still quite smooth, or are only just beginning to show some signs of lacunar absorption. The diploe is hyperemic and congested. Its consistency is decreased, and it contains small fungous growths and droplets of pus. It soon becomes grayish and contains sequestrums. They are generally numerous and small and may remain in the bone for a more or less long time or may be eliminated. The alterations of the bone are especially seen on the external table.

The later changes, which may be regarded as secondary to the necrosis of the bone, consist in the replacement of the bone marrow by granulation tissue, with absorption, erosion and finally disappearance of the bony trabeculae of the diploe. The outer and inner tables withstand the eroding action till a still later period, so that extensive sheets of granulation tissue develop between the still intact, though lifeless, tables. The blood vessels contain thrombi more or less infiltrated with pus cells, and signs of perivascular inflammation accompany the thrombosis when it progresses in advance of the general bone disease.

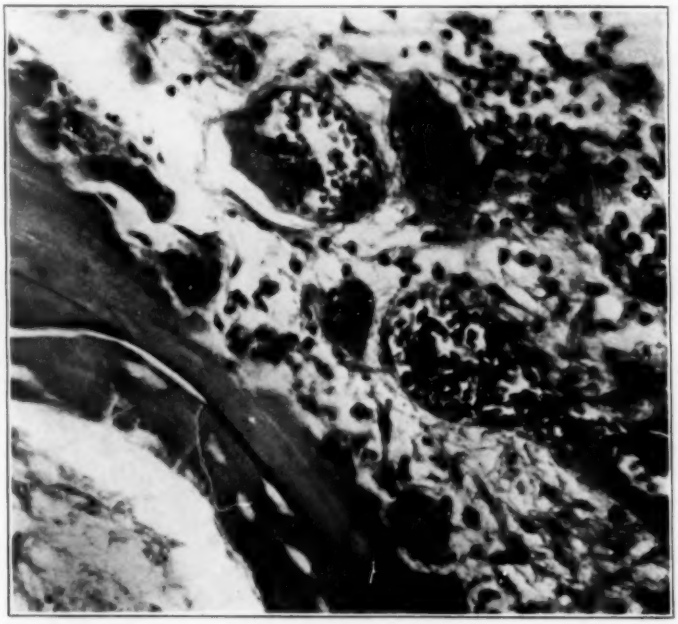

Fig. 3.—Higher power picture of the periphery of one of the diploic spaces, showing in greater detail the osteoclastic destruction of the cranial bone; × 180.

The lesions are seldom confined to the bones, but the integuments become inflamed and infiltrated with pus. A case is described in the literature by Smith [14] in which a segment of skull with its covering of scalp exfoliated in one piece.

The dura mater is always affected and becomes thickened and granular throughout the entire extent of the lesion of the bones. If the lesions do not evolve too rapidly, adhesions are formed in the arachnoid and the brain is protected against encephalitis. But once the natural resistance is overcome, the infection may reach the pia mater and cause

14. Smith: Tr. Clin. Soc. London **3**:163, 1870.

any of the varieties of meningitis, or the suppuration may extend to the brain and the large cerebral sinuses. The latter seems to be the most common complication.

In cases in which general blood infection occurs, the viscera show lesions of a general infection (pyemia). The liver may be increased in size and may show amyloid degeneration. The spleen becomes hypertrophied. The lungs show nodules of hepatinization and bronchopneumonia.

## PATHOGENESIS

According to the pathogenesis involved, cases of osteomyelitis of the skull can be divided into three groups: primary, hematogenous and extension cases.

### PRIMARY CASES

In common with the usual forms of osteomyelitis of the long bones, and to a much less extent, osteomyelitis of the skull is at the present time a comparatively rare phenomenon as a primary disease of the skull, because it can result only as a consequence of trauma.

*Traumatic Cranial Osteomyelitis.*—In 1923, Kallenbach could gather from his own experience only five cases of osteomyelitis of the skull which followed trauma. In one case a blow resulted in a wound which, having apparently healed, opened some days later and discharged; bare bone was felt. In another patient the scalp wound suppurated, and involvement of the bone was established on the twelfth day. In the other three cases it is not definitely established that the mechanism was a primary infection of the bone.

My own experience includes one case in which the trauma was an operative one—an osteoplastic craniotomy; except for this case, the total of this type that I have seen does not number more than two or three in an experience of twenty years.

In accordance with the manner of application of the trauma, and because of peculiarities essential to the latter, one distinguishes the following forms: civil injuries, i. e., falls, blows, etc.; gunshot injuries, including civil and military practice; and osteomyelitis following operative manpulation, i. e., craniotomy of various kinds, etc.

Gunshot wounds form a class by themselves and will not be discussed in this communication. The essential differences between gunshot wounds in civil life and during a military emergency are threefold: (*a*) the depleted and exhausted condition of troops on the battle line, (*b*) the enormous increase in environmental contamination (usually of a fecal nature) incident to active warfare in the field, (*c*) the large size and complexity of the wounds—almost always complicated with intracranial injury, the dominance of which makes for naught any infection of the skull bone—and (*d*) the enormous mortality. It was learned during the last war that the best prophylaxis is an efficient débridement.

Operative infection occurs so rarely nowadays as to be of negligible importance. The usual course of affairs is illustrated by the following personal experience:

In a patient on whom I did an osteoplastic craniotomy, a local infection developed in the wound and was discovered at the first dressing. A very protracted healing followed, which terminated only after a small sequestrum was discharged from the sinus. (Private records.)

In this communication the main concern is the ordinary forms of civil injury to the head. The correct conception of the pathogenic relationship between a head injury and any resultant osteomyelitis of the skull may be one of two: (1) as primary infection and (2) as a hematogenous infection of the skull.[15]

1. Osteomyelitis may be a primary infection, the result of the direct introduction of organisms into the bone tissue. In such cases, primary osteomyelitis of the skull can develop only when a trauma results in an open wound leading down to the skull, in which the solution of continuity of the tissues extends partially into, or completely through, the thickness of the skull.

Contamination of the wound is the rule; but in modern times the establishment of an infection in the bone tissue and its secondary effects (necrosis due to vascular shutoff) is very rare. This is altogether due to proper methods for débridement of the wounds. In the unfortunate case in which osteomyelitis does develop, the area of bone involved depends on the extent to which the thrombophlebitis becomes established; usually this is relatively circumscribed unless the infection reaches into the diploic veins and a thrombophlebitis becomes established in the latter network. It is a remarkable fact that this should happen on such few occasions.

A particularly interesting case is the following in which the infection took place in the apparent absence of any infection of the nasal accessory sinuses; this was an operative infection. (Unless otherwise noted, the hospital cases are from Dr. Elsberg's service.)

A man, aged 44, had an old fracture of the nasal bone; four months before admission, a plastic operation was performed for the correction of this defect, following which there developed severe pain about the right eye and the right side of the nose and a swelling about the right eye; the latter was incised and drained. Three weeks later another incision was made over the glabella. Three weeks after this, incision and drainage over the right frontal region was performed. The patient had had severe frontal headaches ever since his first operation three months previously. All the wounds continued to drain.

Neurologic examination on admission gave negative results. Intranasal examination revealed a left suppurative ethmoiditis and obliteration of the right frontal sinus due to the old operation and a badly deviated right septum, and a

15. The second alternative is discussed in the section on "Hematogenous Cases."

scarred right ethmoid area. Roentgen examination of the skull revealed osteomyelitis of the frontal bone. Operation was performed, sequestrums removed, and the dura exposed but not entered. The patient continued thereafter to have severe temporal headaches without any positive neurologic findings. Febrile and afebrile periods alternated. A revision of his former wound was done; further sequestrums were removed, and a small abscess over the occipit was incised and drained. The patient nevertheless continued to become progressively worse. Subsequent roentgen examinations showed an extensive osteomyelitis. An exploratory craniotomy was then performed, but no abscess was found. After two weeks more of this septic course, during which time the patient deteriorated more mentally and physically, a last attempt was made to find some intracranial focus. During this exploration the entire frontal bone, on both sides, was found soft, necrotic and fragmented. Aspiration of the brain substance gave negative results. The patient was delirious in the morning of the operation, stuporous later in the day, and died shortly thereafter. Permission for postmortem examination was not obtained. The infection was due to Staphylococcus aureus.

It appears from the literature that the types of operative manipulations done in the presence of nasal and nasal accessory sinus infection, and ordinarily designated by the term "minor" and commonly performed in the practitioner's or specialist's office, are a source of traumatic infection. These include conchotomy, septum operations, polyp extractions, etc., as well as manipulations of even less extent, ordinarily called "treatments." (See section on "Pathogenesis.")

Trauma frequently appears in the clinical records of cases in which it is not the sole etiologic factor, for instance, trauma through the middle ear or through the nasal accessory sinuses, as in ordinary forms of fracture of the skull. An added etiologic factor under such conditions can be the presence of infection in the latter territories; osteomyelitis of the skull under such conditions is, however, practically speaking, unknown. This is undoubtedly so because a flare-up of infection under such conditions commonly results fatally before any bone lesion can develop.

Nevertheless, I believe that primary infection of the skull produced by trauma involving a contiguous area of the skull and of the nasal accessory sinuses undoubtedly occurs oftener than is apparent in the various clinical records. I can remember only one such case in private practice. It must be true that when the patient recovers from the injury only mild forms of bone infection exist, and these are unrecognized in a complex of subjective and objective symptoms which are usually referred to an inflammation of one or more of the nasal accessory sinuses.

A particularly interesting case is the following in which undoubtedly nutritional changes produced by the preceding radiotherapy played an important rôle in addition to the trauma.

In a 48 year old man a blow was sustained to that part of the head where an epithelioma of the scalp had been destroyed by radiotherapy ten years previously.

The scalp broke down and ulcerated, and healing never took place; biopsy showed no malignant condition. On exploration, osteomyelitis was demonstrated in the bone. The bacteriologic content was Staphylococcus aureus. The patient died. Postmortem examination showed, in addition, an epidural and subdural extracortical abscess, with thrombophlebitis of the cerebral veins and sinuses.

### HEMATOGENOUS CASES

The mechanism of the pathogenesis and pathology of hematogenous osteomyelitis in general has been discussed extensively on a number of previous occasions,[16] and an extensive discussion of this subject will not be repeated here. Suffice it to say in résumé that acute hematogenous osteomyelitis is a metastatic lesion during the course of a bacteremia, the latter resulting from a bacterial lesion on a surface of the body which forms the portal of entry for the infection. In this conception a surface of the body includes not only the skin, but also the entire mucous membrane of the alimentary tract, the genito-urinary tract, etc. The common surface lesions include not only furuncles, carbuncles, etc., on the skin but also easily demonstrable lesions in the tonsils and in other lymphadenoid collections lying in the mucous membrane of the pharynx, as well as less demonstrable lesions, such as those in the Peyer's patches.

The fundamental cause of the spreading of the original lesion in the form of metastatic or subsidiary lesions is an infected thrombus lying in the original area of infection and communicating at some point with the freely circulating blood. Organisms growing on the surfaces of the thrombus are discharged, or minute pieces of the thrombus laden with bacteria break off and are discharged into the circulation and, becoming lodged for various reasons in the vascular network of various parts of the body, give rise to secondary lesions. Bone tissue, because of its peculiarities in vascular structure, seems particularly prone to the blocking of these thrombi-emboli, and the susceptibility to this is particularly increased during the period of growth when the individual bones contain well marked hyperemic areas at the junction of the diaphysis and epiphysis, around centers of ossification, etc.

The various accessory causes, such as trauma, that determine the localization of a secondary focus of infection—fixation point—in a given bone are associated with accidents in the local circulation which facilitate blocking of any bacterial thrombus-embolus. (See section on "Traumatic Cranial Osteomyelitis.") The essential nature of the patho-

16. Wilensky, A. O.: Ann. Surg. **82**:781 (Nov.) 1925; Am. J. Roentgenol. **16**:123 (Aug.) 1926; The Mechanism of Bacterial Infection, Arch. Surg. **13**:228 (Aug.) 1926; Ann. Surg. **84**:651 (Nov.) 1926; **85**:428 (March) 1927; Am. J. Surg. **3**:281 (Sept.) 1927; Treatment of Infection, Arch. Surg. **15**:737 (Nov.) 1927.

logic process that develops at the fixation point is a thrombo-arteritis or thrombophlebitis, and the process in the skull is exactly similar to that in other bones in which a dominating position is assumed by the secondary vascular thromboses which must necessarily occur in such a pathologic lesion. The all important secondary effects that these thromboses produce are disturbances of essential nutrition which lead to the death of certain bone cells and the consequent necrosis of certain areas of bone tissue.

The actual pathogenesis and pathology in osteomyelitis of the skull are exactly similar to those in other bones of the body the seat of hematogenous osteomyelitis. The point of fixation in the vascular channels of the skull develops into a thrombophlebitis. The occlusion of the vascular channel or channels results in the usual deprivation of blood supply and nourishment, and the amount, degree and character of the resultant necrosis is in direct proportion to the number, size or importance of the vascular channel occluded and the amount of available collateral circulation.

In hematogenous osteomyelitis of the skull, gross trauma to the skull is frequently an important item in determining the localization of the infection in the cranial bones. The following remarks should be compared with those made in the section on "Traumatic Cranial Osteomyelitis."

2. *Traumatic Hematogenous Cranial Osteomyelitis.*—The reception of an injury to the head, whether or not it results in a closed or open wound, and whether or not the latter reaches down into the bone tissue, may lead to an osteomyelitis of the skull as a result of a hematogenous infection, in which the trauma functions merely by creating a point of least resistance for the blockage of any pathogenic bacteria circulating in the blood as a result of a temporary or established bacteremia. This results in the ordinary form of acute hematogenous osteomyelitis. Most of the cases in the older literature described as due to trauma belong in this group, although lack of accurate knowledge has caused them erroneously to be termed "primary" cases.

Illustrative cases are the following:

A case in which the patient struck the forehead against a bench during an acute catarrhal condition of the nasal cavities (Donalies [17]).

A case in which an injury to the head was sustained while the patient was in a bath tub (Schmiegelow [18]).

In the hematogenous variety of osteomyelitis of the skull certain differences are discernible for which the physical basis is the situation

17. Donalies: Arch. f. Ohren-, Nasen- u. Kehlkopfh. **75**:199, 1908.
18. Schmiegelow, E.: Monatschr. f. Ohrenh., 1905, p. 582.

of the lesion in the network of diploic veins. In the long bones, the situation of the thrombophlebitis in an arterial trunk results in a localization which determines more or less a fixed area of bone which will subsequently necrose and sequestrate. In the diploic veins of the skull, the open wide venous channels encourage, promote and facilitate a progressive continuation of the thrombotic process in all directions. In other words, the process is not stationary; this corresponds clinically to the tendency for the osteomyelitis to spread over wide areas of the cranium.

In actual practice, the classification of a given case, while usually more or less easily done, is on occasion a most difficult one. Given a case, for instance, in which a severe (gangrenous) inflammation is present in the frontal or other nasal accessory sinus and an osteomyelitis is present in the contiguous portion of the skull, it might easily be that either had preceded and caused the other; that is, it could just as readily be hematogenous, as an extension form of osteomyelitis. Usually the specialistic tendencies of the observer—general surgeon or rhinologist—determine the interpretation, owing to the fact that no sufficiently powerful clinical, laboratory or other evidence can be mobilized to decide the question. I have such a case in mind:

The history was that symptoms resembling those of the ordinary type of rhinitis were present for one day, and that simultaneously one eye became swollen. The temperature on admission to the hospital was 104 F. The first operation was done on the day of admission to the hospital; an osteomyelitis was present in the appropriate frontal bone. Bacteriologic examination of the pus showed Staphylococcus aureus, and the blood culture was positive for the same organism. The patient recovered after a number of operations.

In 1923, Kallenbach [9] was able to find only twenty-two authentic cases of osteomyelitis of the skull in the literature. In seventeen of these there was apparently a hematogenous origin for the infection.

In a case described by Paschen [19] there was osteomyelitis of the right hip joint, of the right clavicle and afterward of the left parietal bone. The time at which the osteomyelitis of the skull began is not known. In Trendel's [10] case, there was disease of both tibiae, both humeri and the left radius and ulna, followed by osteomyelitis of the right parietal bone. The latter began thirteen days after the onset of the osteomyelitis of the long bones. In Scheinziss' [8] case there was an inflammation of the left tibia, right femur, both humeri and, a month later, of the right parietal bone. Two cases of multiple osteomyelitis are also described by Fröhner [10] from the Tübingen clinic. But the route of the infection is not described. In the first, there was osteomyelitis of the occipital bone, the scapula and tibia; in the second, osteomyelitis of the occipital bone with osteomyelitis of both clavicles and the femur. Among these twenty-two cases, there were no metastases in sixteen and metastases in six, but the route of the infection is not described.

19. Paschen, quoted by Kallenbach (footnote 9).

From other sources one can add the following:

BILLROTH.[20]—One case in the temporal fossa after a resection of the elbow, which became infected.

KÜSTER.[21]—One case of osteomyelitis of the frontal bone after a carbuncle of the neck.

VON BERGMANN.[7]—One case of osteomyelitis of the skull after erysipelas.

LEXER.[22]—One case of osteomyelitis of the skull after a furuncle of the knee.

VON BERGMANN.[7]—Two cases of osteomyelitis of the skull without demonstrable cause.

JAYNES.[23]—One case of osteomyelitis of the skull after measles; one case after typhus.

FISCHER.[4]—One case of osteomyelitis of the skull after a "cold." The notes of this case are interesting:

A "cold" had been present for about three weeks in a 39 year old woman, when she suddenly became ill, with a severe chill, high fever, typhoid-like symptoms and pain in the right temporal and parietal regions. About eight days later a painful swelling developed above the right ear. An incision was followed by a discharge of a large amount of pus. The periosteum of the anterior half of the parietal bone was removed, and there were found numerous suppurative foci of pinpoint size. There was a severe edema of the epicranium of the right half of the skull. The left side of the face and the left half of the body were paralyzed. The patient was delirious. Examination of the eyes and ears failed to reveal a demonstrable pathologic process. A radical operation was carried out, following which the patient died in about seven days. The anatomic diagnosis was as follows: purulent osteitis of the parietal bone and purulent pachymeningitis; purulent leptomeningitis of the right convexity of the cerebrum. A microscopic study of a portion of the bone removed by trephination revealed purulent osteitis and suppurative thrombophlebitis of the veins of the bone. Fischer [4] designated this case as primary or idiopathic acute purulent osteitis because the condition was not preceded by trauma to the bones of the skull, and there was no objective finding pointing to tuberculosis or syphilis. No demonstrable pathologic process could be found in the ear.

The records at Mount Sinai contain the following case in which the hematogenous mechanism is undoubted.

In a middle aged man the classic picture of acute osteomyelitis developed in the opposing ends of the tibia and femur, with involvement of the knee. The end-result was an ankylosed knee and with a small discharging sinus, which persisted. Years later a subperiosteal abscess developed over one parietal bone, and bare bone was palpated in the bottom of the wound. There was no other etiologic factor.

Hematogenous infections of the bones of the skull occur in the following associations:

1. Cases following the ordinary local form of infection, as after a carbuncle.

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20. Billroth: Chir. Klin., 1871, p. 76.
21. Küster, E.: Ein chirurgisches Triennium, Berlin, 1876, pp. 71 and 78.
22. Lexer, E.: Centralbl. f. Chir. (Ref) **22**:947, 1895.
23. Jaynes, M.: De ostéomyélitis des os du crâne, Thèse de Paris, 1887.

2. Cases occurring during or following the infectious diseases, as in the following examples:

Among the cases collected by Kallenbach [9] in which the cause was reported, one each was caused by typhoid, influenza, erysipelas, measles and angina; also one was caused by a "cold." Osteomyelitis of the skull developed four months after the typhoid, two weeks after the influenza and a few days after the beginning of the erysipelas, measles and "cold."

3. Cases due to some temporary bacteremia, the primary cause of which is undiscoverable.

4. Cases of osteomyelitis of the skull occurring in patients who have had osteomyelitis of the long bones for a long period of time. The bacteremia, to the intermediation of which the skull focus is due, is more or less intermittent and chronic, and it is more probable, though not certainly so, that it is derived from one or other of the preexisting bone lesions, rather than from the original primary lesion to which all of the osteomyelitis foci are secondary. At any rate, this has been my experience.

*Relation to Other Foci of Osteomyelitis.*—In most of the reported cases other foci of osteomyelitis coexisted, preexisted or followed the development of osteomyelitis of the skull. I have been able to find one case in the literature in which a second focus developed after the full development of osteomyelitis of the skull. This was in a case reported by Lexer [22] in which on the day after operation for osteomyelitis of the right frontal bone metastasis developed in the right calcaneus.

*Symptomatology.*—The clinical picture in hematogenous infection of the skull is similar in its early stages to that of similar forms of osteomyelitis in general.

In the very severe forms of illness in which hematogenous osteomyelitis of the skull is part of the clinical picture, the severe manifestations—fever, chills and other signs of general infection, including positive blood cultures—are not necessarily to be associated exclusively with the lesions of the cranial bone. All too frequently the skull process is quickly associated with intracranial complications, and it is more to the point to associate the severe clinical manifestations with these rather than with the bone infection. Commonly, it is clinically manifest that the osteomyelitis of the skull is but an incident in a complex, the essential characteristic of which is a general infection of the body.

In the cases of osteomyelitis of the skull of moderate severity, as in all cases of osteomyelitis, there are general symptoms such as fever, chills, etc. Generally speaking, a focus of osteomyelitis is present with well marked local signs and symptoms but without any clinical signs of a general blood infection. A bacteremia is not present. The physical basis for this variety lies (*a*) in a primary and temporary bacter-

emia, (*b*) in the development of a fixation point in a bone and (*c*) in the subsequent spontaneous disappearance of the bacteremia.

In actual practice, the illness commences suddenly, sometimes spontaneously, at other times after an injury often slight in nature. There are malaise, local pain and fever often accompanied by an initial rigor; but when the patient comes under observation he does not present the aspect of extreme illness usually observed in an acute infection of any of the other bones of the body. The grade of these symptoms corresponds to the grade of the local lesion and the extent of the lesion. The outer or inner table only may be affected, or the whole thickness of the bone may be diseased.

In the cases in which the external table only is involved, signs commence to be discernible at the actual seat of the disease almost immediately. The signs consist in the development of an indefinitely demarcated and widespread edematous swelling and tenderness over the appropriate part of the skull. This swelling is rarely detected before the second or third day, and in many of the recorded cases not until later. The swelling may spread in any direction, and a most striking characteristic is the widespread area of the soft parts affected compared with the extent of the bone disease. Presently and quickly these swellings undergo liquefaction, and they are recognizable as subperiosteal (subepicranial) and subcutaneous abscesses of the scalp.

In the cases in which the internal table is involved alone, these local symptoms do not appear; one only has the subjective symptom of pain. Deep-seated fixed pain is, at first, the only sign of mischief; there is no swelling of the soft parts so long as the outer table of the skull remains unaffected, and the patient may perhaps die without there having been the slightest suspicion of the exact state of the bone.

Pain also takes the guise of a diffuse headache with a slightly more definable area over the local disease where the pain is intensified. The pain persists and increases and is controlled with difficulty by the usual means. Headache seems more marked when the internal table is involved to the largest extent or to the exclusion, apparently, of the external table; this is so because of the formation of extradural (subperiosteal) abscesses and their comparative intracranial compressive effects. Practically speaking, this is the entire symptomatology of osteomyelitis of the skull per se.

In superficial osteomyelitis of the bones of the skull, the suppuration, of which there is generally speaking no very great quantity, finds a ready outlet through openings in the skin. But where the bone is perforated in its whole depth, retention of pus may occur, and the latter accumulates between the bone and the dura mater; a small portion only makes its way toward the skin, which, if unbroken, will present an indolent, apparently well circumscribed swelling, the main characteristic

of which is that it disappears under slight pressure but soon reappears, more or less quickly according to the position of the patient's head. When this swelling is opened, the pus flows in much larger quantities than would have been expected from the apparent size of the abscess; its escape is not influenced by pressure, but it may be made to stream out by a forced expiration, the mouth and nose being closed.

In the late stages, the clinical picture is distorted, and the symptom complex referable to the bone lesion itself is lost in more dominating evidences of intracranial lesions which secondarily complicate the osteomyelitis. These will be discussed in the section on "Complications."

### EXTENSION CASES

Most of the cases of cranial osteomyelitis that one sees in hospital and private practice should be classified as extension cases. By that I mean that the osteomyelitis of the cranial bones is due to a spontaneous extension of the inflammatory process in the vascular or lymphatic channels, singly or combined, through contiguity of tissue into the skull bones from a focus of infection in a definite anatomically defined area contiguous to the bone, i. e., from a frontal sinusitis, etc.

The subgroups are as follows: (1) extension from an infection in the soft parts, (2) extension from a focus of osteomyelitis in the superior maxilla, (3) extension from a focus of infection in any or all of the nasal accessory sinuses: frontal, ethmoidal, sphenoidal and antral, and (4) extension from a focus of infection in the otologic apparatus.

*Extension from an Infection in the Soft Parts.*—Extension from an infection in the soft parts to the bones of the skull in the absence of an incomplete or complete fracture seems never to occur or to occur with extreme rarity. Kallenbach's [9] figures are most interesting:

In a period of ten years, ninety injuries of the soft parts of the head were treated, none of which led to osteomyelitis of the skull. Fifty-five injuries of the skull were also treated, among them twenty-two complicated fractures, none of which resulted in osteomyelitis. There was no osteomyelitis of the skull in twelve cases of erysipelas of the head, three cases of phlegmon of the head, two of abscess of the head and two of furuncle of the head.

I have had one experience of this kind.

About ten years ago, I saw a man in consultation in whom a gangrenous infection of the scalp was present. The etiology was obscure. At the time I saw him, the necrotic part of the scalp had separated for the greatest part of the involved area; the cranium lying directly underneath was also necrotic, and numerous small sequestrums could be picked away.

*Extension from a Focus of Osteomyelitis of the Superior Maxilla.*—The physical connection of the superior maxilla with the cranium at

the articulation between its nasal process and the frontal bone makes it possible for an osteomyelitis of the superior maxilla to extend into the cranium. This is possible in the group of cases of osteomyelitis of the superior maxilla which occur in nurslings and infants as well as in a large group in which an infection is present in the antrum and in the bone, and in which it is sometimes difficult to say which of the two is primary. This part of the problem is discussed more fully in the section on antral disease.

*Extension from a Focus of Infection in the Nasal Accessory Sinuses.*—There will be no attempt made to discuss the essential nature of nasal accessory sinus disease as this is not my subject. Only that part of it that seems necessary to the proper explanation of the mechanism by which osteomyelitis of the skull bones complicates accessory sinus disease will be included. In considering this subject, it is to be remembered that not infrequently caries and necrosis of portions of the bony wall of the nasal accessory sinuses occur as part of the pathologic process incident to sinus disease itself; the bone involvement is strictly limited in extent to the area of the latter and directly underlies the affected portion of the mucous membrane. This is the so-called "sinusitis abscendens." It shows little tendency to spread beyond the limits indicated, and surgical intervention of a comparatively simple kind results in a cure. This type and variety of osteomyelitis is also not included in this communication.

Up to the present time, accurate scientific knowledge concerning the pathogenesis and mechanism of osteomyelitis of the skull complicating accessory nasal sinus disease is mostly due to the work of Schilling,[24] Röpke,[25] Gerber[26] and Luc.[5] A résumé of the available literature of importance was made in 1913 by McKenzie,[27] who collated the knowledge of the subject up to that date, the important contributions having been made from German and French sources. The original paper of Schilling[24] contained nine cases; Gerber[26] added twenty, and Luc increased the total number of reported observations to thirty-nine. McKenzie[27] added seven cases. Burger[28] had one case of osteomyelitis of the frontal bone in a total of nine cases of accessory sinus disease with intracranial complications—this in a large private practice of over

24. Schilling, R.: Ztschr. f. Ohrenh. **48**:52, 1904.

25. Röpke, F.: J. Laryng., 1899; Verhandl. d. deutsch. otol. Gesellsch., 1907, p. 162.

26. Gerber, P. H.: Die Komplikationen der Stirnhohlentzündungen, Berlin, S. Karger, 1909.

27. McKenzie, D.: J. Laryng. **28**:6, 79 and 129, 1913.

28. Burger, in Denkler and Kahler: Handbuch der Nasen-Ohrenheilkunde, Berlin, Julius Springer, 1926, p. 905.

thirty years' extent. In 1926, Bulson [29] was able to find only fifty-five cases in the literature of the preceding thirty years. The figures do not indicate at all accurately the numbers of these cases that have and do continue to occur in practice; but, I believe, they reflect fairly accurately the fact that osteomyelitis of the skull as a complication of nasal accessory sinus disease is relatively uncommon.

Between 1924 and 1931, twelve patients were admitted to Mount Sinai Hospital with some form of osteomyelitis complicated by nasal accessory sinus disease.

The cases at Mount Sinai were distributed according to age as follows:

| | |
|---|---|
| Up to 10 years | 3 cases |
| 11 to 20 years | 3 cases |
| 21 to 30 years | 1 case |
| 31 to 40 years | 1 case |
| 41 to 50 years | 2 cases |
| 51 to 60 years | 2 cases |

Most of Burger's [28] patients were between 11 and 30 years old. In Gerber's [26] twenty-nine cases, the distribution according to age was:

| | |
|---|---|
| 0-10 years | 1 case |
| 11-20 years | 4 cases |
| 21-30 years | 11 cases |
| 31-40 years | 3 cases |
| 41-50 years | 3 cases |
| 51-60 years | 0 cases |
| Over 60 years | 1 case |

In the observations up to now, the female sex preponderates. The ratio to the male sex is 8:1 according to Schilling,[24] 11:5 according to Röpke,[25] 16:9 according to Burger [28] and 13:14 according to Gerber.[26] Gerber does not believe that from these figures one may draw a conclusion regarding the preponderance of the female. At any rate, this seems to be of little importance.

*Location of Original Sinusitis.*—As regards the accessory sinus in which the infection originated, it must be remembered that in clinical practice there seems to be no limitation of the infected area to any regional group of sinuses; indeed, the usual thing is to find a diffuse process involving all of the accessory sinus groups. And, if, as sometimes happens, there seems to be a starting point for the infection at some particular point, the spread from the latter to the others is extremely rapid. It would be better to say that the sinus infection, although multiple, seems to exhibit greater manifestations in one or the other groups of nasal accessory sinuses.

29. Bulson, A. E.: Osteomyelitis of the Frontal Bone as a Complication of Frontal Sinusitis, J. A. M. A. **86**:246 (Jan. 23) 1926.

With these criteria in mind, it would, then, be proper to accept McKenzie's [27] figures in which he reports the proportions of the cases of osteomyelitis of the cranium as having occurred forty-five times as a consequence of frontal sinus disease as opposed to three times as a consequence of antral disease, these figures being based on the total number of forty-eight cases.

McKenzie [27] was able to find but one case originating in the ethmoid cells—a case of van den Wildenberg.[30] In this case a small sequestrum of the os unguis was first removed, and fourteen days later a large sequestrum comprising the crista galli and the lamina cribrosa. From observations to be detailed subsequently, I am inclined to agree with van den Wildenberg [30] and to disagree with McKenzie,[27] who wishes to classify this also as having originated in the frontal sinus. In this con-

Fig. 4.—Anatomic relationship of the various sinus groups. *A*, anteroposterior section; *B*, transverse section; *1*, sphenoid group; *2*, ethmoid group; *3*, antrum; *4*, orbit. (After Katz and Blumenfeld: Handbuch der speziellen Chirurgie des Ohren und des oberen Luftwegen, Leipzig, 1923.)

nection the case of Sir St. Clair Thomson,[31] to which McKenzie makes reference, had better be omitted from the discussion at present inasmuch as the mechanism was complicated by the performance of an operation.

The experience of other surgeons varies. Thus, Jansen [32] in ten instances, Röpke [25] in thirty-seven, Killian in sixteen and Luc [5] in four found the ethmoidal cells affected along with the frontal sinus. Walker-Downie [33] noted ethmoidal disease in five of six cases. On the other hand, Lermoyez,[34] in thirty-six instances in which the frontal sinus was

30. van den Wildenberg, quoted by McKenzie (footnote *27*).
31. Thomson, St. Clair: Lancet **2**:431, 1905.
32. Jansen, A.: Arch. f. Laryng. u. Rhin. **6**:355, 1893.
33. Walker-Downie: Glasgow M. J., March, 1899.
34. Lermoyez: Ann. d. mal. de l'oreille, du larynx **28**:593 (Nov.) 1902.

affected, found only two with associated ethmoidal disease; while Herbert Tilley [6] in twenty-five diseased frontal sinuses noted six with ethmoidal suppuration. Milligan [35] described disease of the ethmoidal cells in eighteen of forty-one cases, while of twenty diseased frontal sinuses, observed by Turner,[36] the ethmoidal cells were also affected in twelve. In Wertheim's [37] postmortem observations, the ethmoidal cells were found affected in seven of twelve cases. In a total of 206 instances in which chronic suppuration of the frontal sinus existed, the ethmoidal cells were implicated in 117, i. e., in 56 per cent.

Among twelve cases of osteomyelitis of the skull after nasal accessory sinus disease in the records at Mount Sinai Hospital, the distribution of the original sinus disease was as follows:

Fig. 5.—Diagrammatic representation of one of the typical sequestrations that occur in the ethmoid group of cases.

| | |
|---|---|
| Frontal | 6 times |
| Ethmoid | 2 times |
| Sphenoid | 2 times |
| Frontal and ethmoid | 1 time |
| Sphenoid and ethmoid | 1 time |

I was unable to find any case of osteomyelitis of the skull after disease of the antrum in the records at Mount Sinai Hospital.

It is difficult to assign a cause for the appreciable variance in the individual compilations of cases. One of the things to be remembered

35. Milligan: Brit. M. J., 1905, vol. 1.

36. Turner: Edinburgh M. J. **17**:231, 1905.

37. Wertheim, E.: Arch. f. Laryng. u. Rhin., 1901, vol. 10.

is that the differentiation of the areas that seem to bear the major part of the infection in the general range of the nasal accessory sinus groups is always more or less dependent on the individual interpretation of the objective findings. This could account for the differences in the available statistics.

*Varieties of Sinusitis.*—Osteomyelitis of the skull follows both the acute and the chronic variety of nasal accessory sinusitis. It is altogether likely that even in cases of chronic sinusitis, the occurrence of the bone complication is always in association with an acute flare-up of infection and a spread of the latter into new areas. The only possible exceptions to this statement are found in the simple perforations. See the paragraphs relating to this.

*Bacteriology.*—The bacteriology of osteomyelitis of the skull under the conditions discussed in this communication must necessarily be somewhat uncertain as the bacteriologic findings frequently must show contaminations with other organisms, the habitat of which under normal conditions is the nose and the nasal accessory sinuses. The usual bacteriologic findings described in the literature include Staphylococcus aureus, streptococci and pneumococci. The statement is made by Skillern [38] in discussing Woodward's [39] paper that the cases due to Staphylococcus aureus all progress well and that those due to the streptococcus and the pneumococcus are all fatal. The observation is apparently not sufficiently supported by bacteriologic evidence and needs considerable confirmation before it ought to be accepted.

In the cases at Mount Sinai Hospital the available bacteriologic data in the cases of cranial osteomyelitis derived from nasal accessory sinus disease are as follows:

| | |
|---|---|
| Staphylococcus aureus | 1 time |
| Staphylococcus aureus and streptococcus | 1 time |
| Staphylococcus albus | 1 time |
| Streptococcus | 1 time |
| Streptococcus haemolyticus | 2 times |
| Pneumococcus | 1 time |
| Friedländer bacillus | 1 time |

*Varieties of Osteomyelitic Bone Lesions Found.*—In the literature the varieties of osteomyelitis of the skull that complicate nasal accessory sinus disease have been differentiated and classified on the basis of the extent of the lesion and the rapidity of spread of the pathologic process. This form of classification seems to be a good one and will be followed in this communication also. Clinically, the following are found:

38. Skillern, R. H., in discussion on Woodward (footnote 39).

39. Woodward, F. D.: Osteomyelitis of the Skull, J. A. M. A. **95**:927 (Sept. 27) 1930.

1. Perforating Lesions: In a certain number of the cases this form is associated with insufficient or absent drainage from the normal ducts, and the character of the pathologic process leads one to believe that the process is just what its name implies—a simple perforation. It is questionable whether this form ought to be classified as osteomyelitis; personally, I do not think so.

Perforation is quite common, however, with well marked and more widely spread evidence of true inflammation of bone and of necrosis and sequestrum formation. In these, the diagnosis of osteomyelitis is never in doubt; and the matter of the perforation—in contradistinction to the type just described, in which it is just an attempt on nature's part to secure drainage—is a matter of little importance in the total clinical and pathologic picture.

Perforations are found to complicate both the acute and the chronic type of accessory sinus disease.

2. Localized Lesions: In this variety the tendency is exhibited for the lesion to remain relatively localized and the development of the process is relatively slow, taking months and sometimes years. Exacerbations of infection are, however, very common, and in such an exacerbation the tendency of remaining localized may be lost; then the process spreads with great rapidity over a large part of, or the entire, skull, as is characteristic of the unrestricted variety to be immediately described.

3. Spreading and Diffuse Lesions: There is a certain amount of overlapping between the cases in this group and those in the preceding group, and the physical characteristics of the pathologic process in the cases in this group frequently and commonly also include those of cases in the preceding groups. Clinically, the manifestations may or may not begin with the milder symptoms of the cases in groups 1 and 2; but the great differentiating factor consists in the fact that the relatively benign characteristics of a localized lesion are lost, and the spread of the osteomyelitis becomes unrestricted and extends to the major portion or to the entire extent of the cranium. One must distinguish the diffuse form from the circumscribed form of osteomyelitis, which has a tendency to heal. The diffuse form has a tendency to spread over the entire skull and presents an almost absolutely unfavorable prognosis.

Relative lack of constitutional resistance and relative extreme virulence of the infecting organism have furnished the explanation why one patient does, and the others do not, develop osteomyelitis under apparently precisely similar conditions. The process may seemingly be a unilateral one and limit itself to the bones of one half of the cranium, or, more commonly, it spreads on both sides of the skull. The development of the diffuse form of the osteomyelitis or its extension from more localized forms may occur rapidly, especially in young patients, or, on the contrary, months may be required for the process to evolve.

In Tilley's [6] case, a most extreme one, the process spread upward over the entire vault of the cranium and then downward on each side to and including the petrous pyramid.

*Pathogenesis in Cases Following Nasal Accessory Sinus Disease.*—The nature of the illness and of its origin in an infection of the nasal accessory sinuses is such as to prevent one from securing specimens of the lesion that would demonstrate the early stages when the transmission of the pathologic process occurs into the bone tissue. Beliefs recorded in the literature regarding the paths and the methods of propagation into the bone tissue are therefore necessarily assumptions based on clinical observations and pathologico-anatomic evidence obtained from specimens in a late stage of the lesion.

In the literature, three methods of infection have been suggested:

1. The infection is described as a direct invasion by the organisms of infection of the canalicular and medullary spaces of the bone tissue from the inflamed area of the lining mucous membrane of the given nasal accessory sinus. Preference is given entirely to this method by McKenzie,[27] and, only under certain conditions, by Schilling (i. e., when the diploic tissue abuts on the wall of the frontal sinus, as, for example, in the neighborhood of the upper recess).

McKenzie [27] is inclined to minimize the part played by the diploe of the bone in relation to the sinus, so emphasized by the continental authors, who contend that the proximity of the diploe to the diseased cavity, or its surgical exposure, lays it open to infection. While he believes that the infection may be able to spread more rapidly once the diploe has been reached, he holds that diffuse osteomyelitis is not limited in its spread to diploic bone only.

2. Another group of observers describe the infection as spreading to the bone tissue by the small veins of the mucous membrane of the accessory sinuses, which in turn communicates with the diploic veins. In Laurens' [40] case, it was possible to demonstrate the thrombosis of the diploic veins far in advance of the maturely developed lesion in the skull. It is generally believed that the unrestricted extension of the osteomyelitis in the cranium is due to this variety of mechanism.

3. McKenzie [27] speaks of a "general advance" of the pathologic process which, to him, does not seem to select any particular path. As evidence for this conception, he cites Wylie's case in which bacteria were demonstrated in the haversian canals and under the periosteum, as well as in the diploic spaces and tissues. This suggestion is not difficult to understand. It probably refers to comparatively late cases in which the pathologic process is so widespread in the microscopic picture as to give

40. Laurens, quoted by McKenzie (footnote 27).

the impression that all available paths are being utilized in the spread of the process. This, of course, does not give the true picture.

All three of these methods of spread of the infection are necessarily correct in the observation that the essential part of the process is the spread into the diploic veins. In the light of modern conceptions of disease and of bacteriologic and pathologico-anatomic knowledge, I believe that the following statements may be taken as correct:

There is absolutely no clinical or laboratory evidence to show that the occurrence of the osteomyelitis as a complication of nasal accessory sinus disease is ever due to a hematogenous infection, i. e., that a bacteremia first occurs with the primary lesion in the mucous membrane of any of the nasal accessory sinuses, and that the osteomyelitis is a secondary (metastatic) lesion therefrom. The clinical evidence bears abundant proof, and this is borne out by anatomic and histologic studies (Schilling,[24] Laurens,[40] Wylie [41] and others) that the osteomyelitis of the frontal bone or of the skull is due to (*a*) either a spontaneous extension of the pathologic process along contiguous structures and paths, (*b*) or a direct primary infection of bone tissue during the course of some operative trauma; that is, cases of osteomyelitis of the skull complicating nasal accessory sinus disease are either extension cases or primary cases of osteomyelitis. (See the section on "Traumatic Cranial Osteomyelitis.")

(*a*) Spontaneous Cases: In the cases in which the osteomyelitis is a spontaneous complication, the mechanism of the extension of the process into the cranial bone must necessarily depend on two factors: (*a*) On the bacteria involved in the infection with especial reference to the relative preponderance of virulence of the organism and of the opposing strength of natural resistance. This is important because, otherwise, it might be difficult to explain the occurrence of the osteomyelitis in one patient and its nonoccurrence in others, in all of whom all of the other factors are seemingly identical. (*b*) On the character of the anatomic structures involved with special reference to the structure of the osseous tissue and the arrangement of the arterial and venous network.

According to Gray in his "Anatomy of the Human Body":

> The flat bones of the skull are composed of two layers of compact tissue enclosing between them a variable amount of cancellous tissue. These layers are the outer and inner tables of the skull. The outer one is thick and tough; the inner one is thinner, but of denser structure, and more brittle (i. e., the vitreous table). The intervening cancellous tissue is the diploe.
>
> The walls of the frontal sinuses are composed of thin plates of compact bone which make up the anterior, posterior and superior walls of the sinus. Only where the superior and anterior walls meet to form the superior recess does the compact tissue divide into two tables to include a diploe. Just how far the diploe

41. Wylie, A.: Lancet **1**:178 (Feb. 1) 1919.

extends into the superior and anterior walls is an individual matter; but only in exceptional cases does the diploe extend into these walls for any appreciable distance.

The structure of the irregular bones at the base of the skull is of two varieties. At certain areas, notably where the body of the sphenoid articulates with the occipital, the structure resembles that of other irregular bones, such as the vertebrae: a peripheral layer of compact tissue surrounds a core of cancellous bone. Elsewhere in these bones, the structural masses consist of a series of cellular chambers formed by thin bony plates in which cancellous tissue is for practical purposes absent. At any rate, except at the points indicated there is no direct connection between the cancellous tissue of these bones and the cranial diploe.

These anatomic facts provide the physical basis for the variety of clinical lesions which occur spontaneously as follows:

In simple perforation the chances of the infectious process, under pressure of retained pus and insufficient drainage from the sinus, perforating at any other part than through the thin, bony, plate-like walls is relatively rare. The chances of the perforation in the thin, bony plate lying in an area bearing diploic structure depends on the individual distribution of diploe and is relatively very little. This is borne out by clinical observations and anatomic studies. Simple perforation is always seen through the thin, bony, plate-like walls; perforation elsewhere is usually an incident in a much more widely spread area of osteomyelitis; penetration into the diploe is a much more unusual phenomenon and is always the forerunner of extensive areas of osteomyelitis, and the relatively greater numbers of this complication occurring with frontal sinus disease than with disease in any of the other accessory sinuses are due to the relative and actual sparsity of physical connection between any diploic tissue in the bony walls of the latter accessory sinuses as opposed to the direct connection of the frontal diploe with that of the rest of the cranium. Osteomyelitis is produced in this way by the mechanical introduction of the infection into the diploe.

Other forms, or more extensive forms of osteomyelitis occurring spontaneously with accessory sinus disease, are due to extension of a phlebitic lesion along the vascular channels into the diploe.

According to Gray:

The diploe of the cranial bones is channeled in the adult by a number of tortuous canals, which are lined by a more or less complete layer of compact tissue and contain a network of veins.

The latter are large and capacious, their walls being thin, and formed only of endothelium resting upon a layer of elastic tissue, and they present at irregular intervals pouch-like dilatations, or culs-de-sacs, which serve as reservoirs for the blood. These are the veins of the diploe; they can only be displayed by removing the outer table of the skull.

As long as the cranial bones are distinct and separable, these veins are confined to the particular bones; but when the sutures are united they communicate with each other and increase in size.

As regards the spread of infection by the venous channels, in many instances numerous communicating veins are to be seen with the venous channels in the diploe. Once infection has traveled along these channels into the diploe, the conditions are very favorable for an extension of the inflammatory process further along between the tables of the skull. This favorable condition in the diploe for the extension of the infection has been definitely proved pathologico-anatomically by several observers (Schilling,[24] Laurens [40] and others). The older the patient, the less barrier there is to the extension of the infection, and, as McKenzie [27] and others have pointed out, in adult life there is a direct continuity of osseous structure between the contiguous bones of the skull and of the diploic veins which traverse the sutures of the skull. Diffuse and rapidly spreading forms of osteomyelitis must necessarily always occur by way of the vascular channels, as once the infection has penetrated into the vascular network no efficient obstacle is present to the further spread of the infection along the veins past the sutures and from one cranial segment to the others.

(*b*) Postoperative Cases:[42] It would be well to understand at the outset that although the literature speaks at length of cases in which this complication occurs spontaneously, this probably occurs in a much smaller percentage than is apparent. For, the term "operation" should include not only those large manipulations ordinarily dignified by the attachment of some surgeon's name, but also all of those minor manipulations (extraction of polyps, etc.) which are not classified as such, but are called "treatments" of one kind or another and are commonly performed in the practitioner's or specialist's office. These, under proper circumstances which are all too commonly present, can be productive of all grades of traumatism to the soft parts and to the vascular channels.

In spite of the fact that in the literature the total percentage of cases in which osteomyelitis of the skull occurs as a complication of nasal accessory sinus disease is approximately 3, the opinion has become prevalent among otolaryngologists that while osteomyelitis of the skull bones is one of the uncommon spontaneous complications of nasal accessory sinus disease, it is one of the commonest serious sequela of operation for the cure of the latter. This statement seems to hold true for the most part for cases of frontal sinus disease. It holds true to a much less extent for cases of ethmoid sinus disease, and possibly not at all for cases of sphenoid or antral sinus disease. The facts in the matter seem to be as follows:

Gerber's [26] communication lists twenty-nine cases of osteomyelitis of the frontal bone or skull complicating accessory sinus disease. In thirteen of these cases no definite etiology is mentioned; in the other sixteen,

42. See section on "Traumatic Cranial Osteomyelitis."

influenza, syphilis, trauma, coryza and measles are mentioned as etiologic factors. I, personally, believe that such etiology did not play a rôle in the production of the osteomyelitis, but rather in the production of the original accessory sinus disease. The important point is that among the sixteen cases cited by Gerber,[26] osteomyelitis of the skull followed some operation on the accessory sinuses ten times—a very large proportion.

McKenzie's [27] statistics cover forty-one cases of osteomyelitis of the frontal bone in which the complication developed spontaneously in twenty-one cases and after some form of operation in twenty cases.

In the Mount Sinai group practically all of the cases of osteomyelitis of the skull complicating nasal accessory sinus disease developed prior to the performance of any operation of the Ogston-Luc [43] or Killian [44] types in the hospital. There is a possibility that in some of them at least, some minor forms of "office" operations had been done previously to the admission of the patient to the hospital. In general, the osteomyelitic process was discovered at the time the first operation was done in the hospital. This experience corresponds with that of Burger.

This discrepancy seems to offer insuperable obstacles to adjudication except on the basis of individual interpretations of operative findings. My personal impressions incline me to agree with those who believe that operation is a frequent precursor of the osteomyelitic complication. An examination of all of the factors entering into the various types of operation for nasal accessory sinus disease seems, therefore, in place.

There are two types of operation:

(*a*) Operations of the Ogston-Luc type consist in opening the frontal sinus through its anterior wall, in careful curetting of its interior, in establishing a large communication between the sinus and the nose and at the same time destroying the anterior ethmoid cells in the region of the nasofrontal duct. Drainage into the nose is ensured through the nasofrontal aperture, and the operation is completed by immediate suture of the skin incision.

Probably no other type of operation has been more generally performed on the frontal sinus, yet because of anatomic structure, clinical evidence has been very much against the performance of an operation that does not permit of thorough inspection of the entire sinus and of the ethmoid cells. In order to bring this about, it is necessary to remove the whole of the anterior wall of the sinus, and also to a greater or lesser extent the floor. By such a procedure one is able to inspect the whole interior of the cavity thoroughly, however large it may be; no

43. Ogston-Luc: München. med. Wchnschr., 1895, no. 28.

44. Killian: Ztschr. f. Ohrenh. **37**:343, 1900; Arch. f. Laryng. u. Rhin., 1902, vol. 13.

recess can escape one's observation; the septum between the two cavities can be examined, and the presence of ethmoid cell extension into the orbital roof will thus not be overlooked.

(*b*) This is the reason and the basis for the modern Killian type of operation. The whole sinus, with its recesses and partitions, is thoroughly inspected, and the cavity is almost completely obliterated by the resection of its anterior and inferior bony walls. Further, by the removal of the ascending or frontal process of the superior maxilla, excellent access is obtained to the ethmoid cells, and a large opening of communication is thus made between the frontal sinus and the nasal cavity, so that good drainage into the nose can be established.

Two factors are constantly present in all cases in which operation is done for nasal accessory sinus disease:

(*a*) Infection is always present, and the operation must necessarily be done through infected territory. The only possibility of preventing this would be to so arrange the steps of the operation as to remove the entire infected area in one segment, a procedure which, while possibly technically feasible, would be unwarranted for any and all other reasons, would result in a deformity of contour that would not be acceptable to either the surgeon or the patient, and would probably yield an enormous mortality. One must content oneself, therefore, with less radical measures—a state of affairs that makes it technically impossible to remove every bit of infected tissue. Foci of infection are, therefore, necessarily left which readily contaminate the newly exposed bone tissue in the operative field.

In those unfortunate cases in which operation is undertaken for the cure of sinus disease, the inflammatory condition is markedly enhanced during the operation. The granulation tissue in the sinus, which has hitherto formed a barrier to the invasion of the organisms, is broken down, and a path is opened, which readily admits of their further spread into the frontal bone.

(b) The second constant factor is operative trauma. The same anatomic studies to which I alluded previously show also why operation for sinus disease is so apt to be complicated by osteomyelitis of the skull. If the operator is not careful, or the anatomic distribution of the diploe is extraordinarily well developed and reaches beyond the usual limits, opening into the diploe by chisel or curet is to be expected and does commonly occur. Infection is then implanted directly into the diploic contents.

An analysis of the cases made by Turner [36] showed that in 74 per cent of the cases in which the osteomyelitis appeared the complication occurred after the sinus was opened and drained (Ogston-Luc type of operation). In 88 per cent of these, death followed a single operation,

while in the remainder more than one operation had been performed, owing to the failure of the first to effect a cure of the suppurative condition. The remaining 24 per cent of the cases all proved fatal after an operation for obliteration of the sinus; in 50 per cent of these, simple opening and draining had been previously performed without success, the more radical method having been a secondary procedure. It is evident, therefore, that a considerably larger proportion of the cases occurred after the Ogston-Luc type of operation than after the operation for obliteration. This general impression is confirmed by Burger.[29]

Consideration of the steps in either form of operation gives an adequate explanation of the results. In the simple (Ogston-Luc) operation, an opening is made into the frontal sinus through its anterior wall. The density of the bone forming the anterior wall of the frontal sinus varies considerably, and anatomic studies have shown that this general area is the one in which the diploic structure is commonly found; whenever, as in some instances, the diploic structure is exaggerated, it spreads downward for a considerable distance. The more the diploe of the walls of the frontal sinus is developed, the greater is the anatomic predisposition for the development of osteomyelitis of the frontal sinus. For this reason, young persons are more predisposed than those of mature age. In the former, the diploe has larger meshes and has a larger supply of vessels than in the latter. Cases in which prior to and during the first operation on the frontal sinus nothing pointed to a disease of the bone, and in which such a disease occurred only after the operation, naturally intensify the feeling that the operation itself was the cause of the infection of the diploe.

The mere chiseling of the anterior wall of the frontal sinus is sufficient to open and to infect the diploe of the frontal bone. This was probably so in the case of St. Clair Thomson and in that of Luc and Lermoyez.

In the radical (Killian type[44]) operation, the complication is not so likely to occur, because one of the points of this type of operation is the retention of as much of the anterior wall of the sinus as is possible, the approach being made through the floor in order to prevent the deformity that accompanies excessive removal of the anterior wall. The floor of the sinus practically never contains diploe, the compact bone tissue of the bony plate does not take up the infection so readily, and the complication therefore appears less often after this type of operation. As a matter of fact, in many of the cases in which this radical type of operation has been done, and in which the osteomyelitis developed, it has been preceded by the simple drainage (Ogston-Luc) type of operation.

Once infection is introduced into the diploe, the physical basis for the localization, the firm lodgement and the spreading of the infectious process depend on the character of the vascular network of the skull and

on whether the infection is lodged ($a'$) in the venous plexus or ($b'$) in an arterial trunk.

($a'$) In the former, a thrombophlebitis becomes established in the venous plexus of the diploe. The character of the osteomyelitis, whether localized or diffuse, the relative rapidity of spread and any other physical characteristics depend on the area of venous plexus involved in the thrombophlebitis, and on the biologic virulence of the infecting organism as opposed to the natural protective powers of the host.

($b'$) In the second group, an injury most probably takes place during the course of the operation to an arterial trunk, and a secondary thrombosis occurs in the latter.

According to Gray:

> The supra-orbital artery arises from the ophthalmic as that vessel is crossing over the optic nerve. Ascending so as to arise above all the muscles of the orbit, it passes forward, with the supra-orbital nerve, between the periosteum and levator palpebrae; and, passing through the supra-orbital foramen, divides into a superficial and deep branch, which supply the integument, the muscles and the pericranium of the forehead, anastomosing with the frontal the anterior branch of the temporal, and the artery of the opposite side. This artery in the orbit supplies the superior rectus and the levator palpebrae and sends a branch inward, across the pulley of the superior oblique muscle, to supply the parts at the inner canthus. At the supra-orbital foramen it frequently transmits a branch to the diploe.
>
> The ethmoidal branches are two in number—posterior and anterior. The former, which is the smaller, passes through the posterior ethmoidal foramen, supplies the posterior ethmoidal cells, and, entering the cranium, gives off a meningeal branch, which supplies the adjacent dura mater, and nasal branches which descend into the nose through apertures in the cribriform plate, anastomosing with branches of the sphenopalatine. The anterior ethmoidal artery accompanies the nasal nerve through the anterior ethmoidal foramen, supplies the anterior ethmoidal cells and frontal sinuses, and, entering the cranium, gives off a meningeal branch, which supplies the adjacent dura mater and nasal branches, which descend into the nose, through the slit by the side of the crista galli, and, running along the groove on the under surface of the nasal bone, supply the skin of the nose.
>
> The frontal artery, one of the terminal branches of the ophthalmic, passes from the orbit at its inner angle, and, ascending on the forehead, supplies the integument, muscles and pericranium, anastomosing with the supra-orbital artery and with the artery of the opposite side.
>
> The nasal artery, the other terminal branch of the ophthalmic, emerges from the orbit above the tendo oculi, and, after giving a branch to the upper part of the lachrymal sac, divides into two branches, one of which crosses the root of the nose, the transverse nasal, and anastomoses with the angular artery; the other the dorsalis nasi, runs along the dorsum of the nose, supplies its outer surface, and anastomoses with the artery of the opposite side and with the lateral nasal branch of the facial.

Injuries to any of these major arterial channels are accountable for those larger, more or less anatomically well defined areas of osteomyelitis

which result in correspondingly similar masses of sequestrated bone. One of these typical clinical entities occurs in the frontal bone. The physical basis for this is undoubtedly injury to the terminal branch of the frontal artery after its emergence through the supra-orbital foramen, which branch supplies, among other structures, the pericardium of the vertical portion of the frontal bone just above the glabella. An arterial lesion of this kind undoubtedly also supplies the physical basis for the lesion described by Smith in which a segment of bone and its corresponding integument exfoliated in one piece. Another example of this type of lesion is the sequestration which occurs in the ethmoid, and for which the physical basis is injury to the ethmoidal arteries. (See under discussion on the frontal and ethmoid groups.)

Fig. 6.—Arterial blood supply of the general frontal and ethmoid sinus regions, including that of the orbit. *A*, anterior, and *B*, posterior ethmoidal arteries; *N*, nasal artery; *F*, frontal arteries; *S*, supra-orbital artery; *IC*, internal carotid artery; *O*, ophthalmic artery; *L*, lacrimal artery. (Tracing from Gray's "Anatomy of the Human Body.")

Operative injury, by itself, whether to the venous plexus of the diploe or to a major arterial trunk, would possibly not be sufficient to give rise to osteomyelitis of the skull. The constant presence of virulent organisms, both normally residing in the nasal and nasal accessory cavities, and also present as the inciting agent of the original sinusitis, provides the necessary and essential element for the establishment of an inflammatory lesion in the bone tissue. The operative injury provides a soil of decreased resistance for the growth and development of the organisms, and in the cases of injury to the arterial trunk establishes areas of bone in and from which nourishment by blood supply has been

eliminated. Operative injury plus infection provides the two factors necessary to give the total clinical picture.

The question of drainage after operation is also important. In neither of Lack's fatal cases was the mucous membrane of the sinus curetted, yet an osteomyelitis of the frontal bone supervened, and death followed from intracranial complications. Tilley [6] blames defective drainage into the nose, coupled with complete closure of the skin incision, as a cause of disaster in these cases. Most surgeons will probably agree with the necessity of establishing free drainage, a point that has from time to time been insisted on by the majority of writers on the subject. In two fatal cases, mentioned by Turner,[31] no sutures were placed in the skin incision, thus ensuring free superficial drainage; in one of these, however, the fatal result is attributed to defective nasal drainage; in the other, numerous ethmoidal cells extending into the orbital roof were overlooked, and bone sepsis was thus set up.

I think that Turner's experience is almost sufficient to show that the question of the drainage itself is not of much importance as regards the appearance of the osteomyelitis. The latter, under such circumstances, probably should be explained on the basis discussed in the section devoted to the spontaneous occurrence of this complication after nasal accessory sinus disease.

*Symptomatology in Cases Following Nasal Accessory Sinus Disease.*—As a general rule, the symptomatology of osteomyelitis of the skull conforms itself to anatomic considerations incident to each sinus group. This is especially so for perforative and localized lesions, and for these reasons the discussion of the symptomatology of these varieties of lesions will be found in the subsequent appropriate sections giving the individual characteristics of each sinus group.

Localized pain and diffuse headache associated in many cases with vomiting are important clinical symptoms. More detailed discussion is found in the individual discussions, especially that related to sphenoid sinus disease.

In severe, spreading and diffuse forms of osteomyelitis of the skull complicating nasal accessory sinus disease, a general similarity of the clinical picture is exhibited by all groups.

Hyperacute cases of osteomyelitis of the skull complicating nasal accessory sinus disease are relatively rare. The clinical picture of the cases in this group is that of a profound general infection: There are marked toxemia and a very severe organic resection. The disease begins with violent chills, and high fever follows; the general condition frequently and suddenly becomes grave, the pulse becomes weak and feeble, the urine is scanty and sometimes contains albumin, diarrhea often

appears, and the patient is prostrated and covered with perspiration. In the most severe cases, death follows in a few hours from the general infection.

In extremely sick patients, alarming secondary intracranial complications develop and the symptomatology of the osteomyelitis is overshadowed by the latter. These will be discussed subsequently and more extensively on another occasion.

A general blood infection (sepsis, septicemia, pyemia) is not commonly demonstrable in uncomplicated cranial osteomyelitis by positive blood cultures. Nevertheless, transient or more prolonged states of blood infection undoubtedly do occur, as in some of the fatal cases lesions are described and are present in organs distant from the seat of the local lesion or its neighborhood, the mechanism for the production of which is surely blood-borne.

Positive blood cultures are uncommon. A positive culture occurred in one of the twelve cases at Mount Sinai Hospital; Staphylococcus aureus was recovered. In another case due to infection by the pneumococcus type I, it was suspected that a bacteremia was present; as the patient died two hours after admission, there was no opportunity to prove this. It is my impression that positive blood cultures occur only when meningitis and other similarly grave intracranial complications occur.

*Clinical Course in Cases Following Nasal Accessory Sinus Disease.*—The course of the disease is generally very protracted and is frequently interrupted by intervals of relative euphoria. In Luc's case there was a period of three months between the last manifestation of osteomyelitis and the first one of pachymeningitis; the entire disease lasted two years; a cure was then obtained, which Luc ascribes to the slight virulence of the streptococci. In general, the development of the entire disease and its clinical picture may take as little as two or three months, or as long as two or more years. In the fatal cases the cause of death is much more commonly the effects of the intracranial complications; much less commonly it is the effect of a general blood infection.

A. Special Characteristics in Cases Associated with Frontal Sinus Disease: Cases of frontal sinus disease have formed the bulk of the cases in which osteomyelitis of the skull has complicated the clinical picture; that they have been the basis for most of the reports to be found in the literature.

In Gerber's [26] series of twenty-nine cases the lesion was present as follows:

| | |
|---|---|
| In the anterior wall | 13 times |
| In the posterior wall | 7 times |
| In the floor | 2 times |
| In all walls | 1 time |

In frontal sinus disease, perforations occur as follows: (*a*) In the anterior wall of the frontal sinus. An abscess then forms over the frontal eminence. The spread of this form of abscess is always upward under the scalp.

(*b*) In the floor of the frontal sinus. A subperiosteal abscess forms that can be palpated as a lump attached to the roof of the orbit. Involvement of the general orbital cavity cannot and does not occur until the orbital periosteum breaks and permits the diffusion of the pus into the orbital cavity. In the late stages, proptosis occurs. This form of abscess never spreads upward under the scalp of the forehead.

(*c*) In the roof of the frontal sinus. An extradural abscess forms. The further spread of the suppuration occurs by tracking between the dura and the bone, and by increasing accumulations of pus when signs of intracranial compression occur or by perforation through the dura when subdural intracranial complications, to be discussed subsequently, occur.

Localized forms of osteomyelitis complicating frontal sinus disease are found as follows:

(*a*) Relatively small areas in the anterior wall of the frontal sinus. These are relatively easily recognized by the swelling over the frontal eminences. The lesion tends somewhat to remain localized and, unless spreading of the lesion occurs, give little cause for concern.

(*b*) Relatively small areas in the superior-posterior recess of the frontal sinus. These are more difficult to recognize, and most commonly presage a later and more widely spread lesion. Intracranial complications occur but not as commonly as in the next variety.

(*c*) Relatively small areas in the upper angle of the frontal sinus. These, as well as those in group *b*, are difficult to recognize clinically, are apt to grow in size and spread rapidly and unlimitedly, are commonly complicated by intracranial lesions (because the diagnosis is made late), and, because of these facts, have a high mortality.

(*d*) A characteristic sequestrum. The sequestrum has the shape of a tennis racket, the narrow part occupying the general region of the internal angular process of the frontal part, the flare spreading obliquely upward and outward in the vertical portion of the frontal bone and lying altogether to one side of the median line.

Most of the diffuse forms of osteomyelitis of the skull occur after frontal sinus disease. The direction of spread of the process in the cranial bones is somewhat characteristic: The general tendency is for the process to spread upward and outward from the region of the appropriate sinus into the vertical portion of the frontal bone; then to the parietal and temporal regions, and finally to the occipital bone. There

is no strict limitation of the process to one side of the skull, and although this is the general rule, involvement of the opposite side by contiguity is common. There seems to be little or no tendency for the osteomyelitis to spread into the base of skull when the other sinus groups are uninvolved.

1. Symptomatology and Clinical Course in Cases of Simple Perforation: In cases of simple perforation through the floor of the sinus, the symptomatology is simple, and a diagnosis is easily made. In a patient with symptoms of frontal sinus disease, the orbital fissure narrows, the orbital content becomes swollen and there is a good deal of tearing. Pain is present, or becomes exaggerated. There is usually no fever.

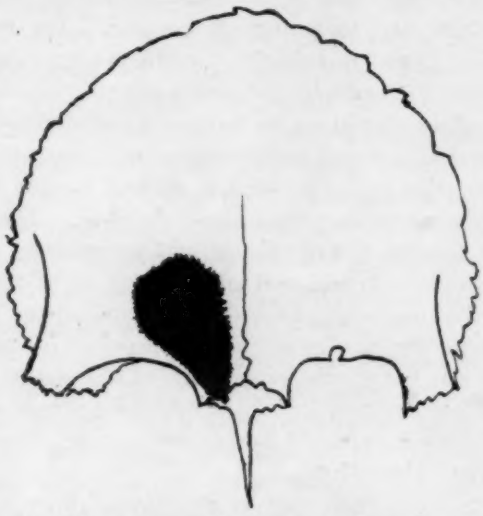

**Fig. 7.—Diagrammatic representation of a typical sequestration seen with frontal sinus disease.**

Frequently a small mass is felt attached to the roof of the orbit, which is a subperiosteal abscess. If the latter is not promptly incised, and if it should rupture into the orbit, a diffuse orbital phlegmon develops.

In cases of simple perforation through the anterior wall, the symptomatology is also not difficult; the region of the glabella becomes swollen and edematous, and an abscess forms under the skin, which either ruptures spontaneously or is incised. In either case, a probe quickly demonstrates an opening leading into the frontal sinus.

I have come across no case in the literature, nor have I personally seen any case in which simple perforation occurred anywhere else than as indicated in the text.

2. Symptomatology and Clinical Course in the Localized Form: In the ordinary case of an insidious development of an osteomyelitis of

the skull complicating a frontal sinus, the suspicion that the latter is developing does not arise for an appreciable interval. In cases in which operation has not been performed clinically the most important symptom is the extension beyond the borders of the frontal sinus of an edematous swelling combined with an actual doughy infiltration, which extends below the scalp and remains constant when there is free drainage of the pus. Multiple subperiosteal abscesses speak for osteomyelitis, especially if there are concurrent general symptoms. This applies more so when the probe below the galea encounters everywhere rough bone. Morel and Hubert [45] compare the osteomyelitic bone with "rotting wood."

If an operation of the frontal sinus has already preceded, then the beginning of the osteomyelitic complication shows itself first in a reddening, swelling and loosening of the scar. The lifting up of it reveals pus. The probe reveals the conditions just described. These symptoms indicate the necessity for a new operation.

At the secondary operations the wound is enlarged by means of new incisions. The skin is found to be swollen and infiltrated and contains islands of suppuration. The friable and necrotic bone is removed. The subadjacent dura mater is fungous and purulent. The limits of the osteitis are not grossly distinguishable and are reached with difficulty. The bone is always thickened, soft and red. If all of the affected portions are removed, the temperature descends and all the symptoms disappear. But more frequently there is only a period of calm, and on the second or third day the wound suppurates. Cicatrization does not take place; the gangrene extends, and the temperature becomes irregular. A new operation again is indicated, and is then usually done in an attempt to get beyond the diseased area.

This same clinical picture may be reproduced three or four times at more or less long intervals, and a cure may finally be obtained, but in most cases the pain is continuous and the swelling of the wound persists.

In the severe rapidly progressing cases, this always occurs with increasing frequency. New subperiosteal abscesses form. Frequently, in the severe cases, the local symptoms decrease, but the general symptoms increase and the entire organism is invaded by a general blood infection. There is severe intoxication of the organism with chills, profuse perspiration, delirium and remittent fever. There is an increase in the size of the liver and spleen. Death occurs from extension of the infection to the brain, sinuses or lungs, regardless of new operations.

3. Symptomatology and Clinical Course in the Diffuse Form: In the diffuse form, there are certain symptoms that are more or less characteristic. The pain is diffuse, and the patient cannot localize it.

45. Morel, L. E., and Hubert, C., quoted by Guisez: Bull. et mém. Soc. franc. d'otol. **1**:1, 1906.

The headache generally is more severe at night, as is the case with all pains of osseous origin. The patient is unable to sleep, and even large doses of opium or narcotics do not relieve the pain. It is generally more marked at the beginning of the condition, but it is very variable. In some cases it does not appear until the end, and it may even be absent.

The swelling around and about the wound is not sharply defined. It may be of a doughy nature, and then it may make one think of an erysipelatous infection. As the process spreads, discrete swellings appear at some little distance; these are subperiosteal abscesses. The skin is red and very tender.

Fever is for the most part continuous, although the curve may fall to normal limits for short intervals only to return promptly. At the onset the temperaure is apt to be very high and of an irregular course. During the course of the disease, when the manifestations are particularly severe, the temperature frequently assumes the characteristics customarily seen in typhoid fever. Chills are not common; they occur only in cases of general infection, frequently indicate the presence of a complicating phlebitis of one of the intracranial sinuses, are present with and without positive blood cultures and are generally of unfavorable prognostic value. There may be terminal hyperpyrexia.

B. Special Characteristics in Cases Associated with Ethmoid Sinus Disease: Inflammatory disease of the ethmoid sinuses is so intimately bound up with disease of the sphenoid and frontal sinuses, and these so commonly occur together, that a separate discussion of this phase of nasal accessory sinus disease, so far as it concerns itself with secondary osteomyelitis of the skull, seems unnecessary. In the sense in which this communication is written, it seems probable that osteomyelitis of the skull occurs with least frequency after disease of the ethmoid sinuses, and then it is probable that associated disease of the frontal sinus exists.

In the cases of diseased ethmoid sinuses, perforations occur as follows: (*a*) into the orbit (an orbital phlegmon results) or (*b*) into the nasal cavity.

With disease of the ethmoid sinus, localized forms of osteomyelitis of the skull bones occur in which the process is more or less limited to the nasal process of the superior maxillary bone, the crista galli and cribriform plate of the ethmoid or the thin bony plates forming the mesial wall or roof of the orbit. In the cases of ethmoid sinus disease the general tendency is for the infection to spread forward and slightly upward in the directions just indicated, i. e., to the lacrimal bone, the nasal process of the superior maxillary bone, the cribriform plate and the crista galli.

Diffuse forms of cranial osteomyelitis do not occur, in my opinion, unless involvement of other sinus groups, especially the frontal, coexist.

The symptomatology of perforation in cases of ethmoid sinus disease is nil when the perforation occurs in the nasal cavities, except for some usually undervalued increase in the nasal discharge. There is a characteristic amelioration of the symptoms. In well marked cases of disease of the ethmoid sinus this should be suspected when these two characteristics are encountered.

In cases in which the perforation occurs into the orbit, the symptomatology is that characteristic of an orbital phlegmon, is sometimes more or less dramatic, and is frequently secondarily complicated by intracranial lesions.

Hubby's [46] case is a good illustration:

> The postmortem examination showed: exophthalmos and pus in the orbit; left lateral sinus thrombosis; left sigmoid and left cavernous sinus thrombosis, but not purulent; necrosis of the wall of the right orbit. There was a one week's history, the infection having apparently begun in the nasal cavities.

C. Special Characteristics in Cases Associated with Sphenoid Sinus Disease: It is probable that cases of sphenoid sinus disease are frequently mistaken for other entities, and experiences are on record where the cases are confounded with disease centered in the frontal or ethmoid sinuses or with foci in the middle ear or mastoid. It seems certain from the reports in the literature that recognition of the development of an acute osteomyelitis in the body of the sphenoid rarely occurs during life; the diagnosis is apparently most commonly made at the postmortem examination.

Owing to this fact the number of cases reported in the literature do not reflect the actual numbers of cases that have undoubtedly occurred, nor the relative frequency to other types of nasal accessory sinus disease. Cases of sphenoid sinus infection usually find their way into the recorded literature because of the bizarre clinical picture; more especially because of the apparently sudden onset of a rapidly fatal illness, which is usually proved later to be but a hyperacute exacerbation of an old infection, and most especially because of the intracranial complications that occur, the apparently sudden appearance of which causes the alarming change in the clinical picture and furnishes these powerful elements that overwhelm the resistance of the patient and gives the fatal character to the illness. The rôle of any osteomyelitis is usually lost in the clinical turmoil.

In 1929, Kramer [47] could find less than a hundred cases of sphenoid sinus disease with complications in the literature. He reported nine cases of this kind from the Mount Sinai Hospital, five of which occurred in the hospital in the preceding year. Among these nine cases,

46. Hubby: Laryngoscope **31**:204, 1921.
47. Kramer, Rudolph: Laryngoscope **39**:573 (Sept.) 1929.

there were two in which frank osteomyelitis of the bone of the skull was present either as a coincidence in the total clinical picture, or as the means by virtue of which other intracranial complications had been brought about.

Kramer [47] supplied the notes of these cases:

A man, aged 50, had a cold in the chest for several weeks; for three days he had had fever; for two days he was restless, delirious, and finally unconscious. Physical examination showed: marked toxemia, signs of meningitis, bilateral early papilledema, vertical nystagmus, an enlarged heart and peripheral atherosclerosis. Lumbar puncture yielded purulent fluid under increased pressure containing pneumococcus type I. Death occurred two hours after admission.

Postmortem examination showed: diffuse meningitis, more marked at the base; right cavernous sinus phlebitis; pus in both posterior ethmoid and sphenoid sinuses; the body of the sphenoid sinus, hemorrhagic and purulent, and a red glazed pharynx and nasopharynx covered with dried purulent crusts. Pneumococcus type I was isolated in the aforementioned lesions.

A woman, aged 55, gave a history of symptoms of five months' duration, which followed a chronic course. There were intracranial manifestations. A diagnosis of a metastatic malignant condition was made at first because of coexistent lesions unrelated to the principal disease process. The examining rhinologist diagnosed spheno-ethmoiditis, and a bilateral operation was performed. The Friedländer bacillus was found in the spinal fluid and in the sinuses. After the intranasal operations, the patient was markedly relieved for two weeks, and the cells in the spinal fluid dropped from 2,400 to 175 and from 89 to 50 per cent polymorphonuclears. Meningitis developed. Intravenous therapy was instituted for sepsis. The patient went into a state of coma, and died.

Postmortem examination showed: purulent meningitis and encephalitis, a large left sphenoid sinus containing creamy, yellow pus and a right sphenoid containing a small amount of pus, as did the ethmoids on both sides. Posterior to the left sphenoid, the medulla of the basisphenoid and basiocciput was soft and friable, with a path of necrotic bone leading from the left sphenoid sinus through the basiocciput perforating into the cerebellar fossa. The dura here was perforated. The surrounding dura was thickened, dull in appearance and covered with pus. The pus was adherent over the perforated dura. A culture revealed atypical bacillus of the Friedländer group.

The pathway of infection was from the larger sphenoid sinus, through the medulla of the basisphenoid and basiocciput, through the dura of the cerebellar fossa and into the pia-arachnoid. There had been temporarily a successful attempt on the part of the meninges to wall off the process in the region of the necrotic cerebellar floor, but this barrier was finally broken down.

I have been able to find the following additional cases in the literature:

EAGLETON.[48]—The patient had had chronic "catarrh" of the nose and throat, bilateral chronic otitis and bilateral acute exacerbation of otitis media. Four weeks later double vision developed. There were general symptoms of general infection, and tenderness of the right mastoid. An intra-oral incision was made

48. Eagleton, W. P.: Cavernous Sinus Thrombosis, New York, The MacMillan Company, 1926.

of an empyema of the sphenoid sinus pointing into the nasopharynx; bare bone was palpated extending upward into the base of the skull. Subsequent exploration and exenteration of the sphenoid and ethmoid sinuses were done. The patient died. Postmortem examination revealed thrombosis and suppuration in the right lateral sinus and jugular vein and bulb.

HOSTON.[49]—The patient suffered from pain over the eyes, purulent secretion from the nose, exophthalmos and paresis of the facial muscles. Death occurred.

The diagnosis made on section was inflammation of the sphenoidal sinus associated with osteomyelitis, necrosis and gangrene of the basilar sphenoid and occipital regions, thrombosis of the cavernous sinus and ethmoid; purulent meningitis, pulmonary abscess and parenchymatous degeneration in the viscera.

GRANT.[50]—In a fatal case of sphenoid osteomyelitis, at autopsy the sella turcica and body of the sphenoid were found to be brown and markedly soft and readily admitted the chisel. The entire body was similarly involved. The other bones were normal.

The postmortem diagnosis was: abscess of the body of the sphenoid, osteomyelitis of the sphenoid, basilar meningitis, cerebral edema, otitis media purulenta, bronchopneumonia, myocarditis, acute splenic tumor, acute glomerular nephritis and toxic nephrosis and passive congestion of the liver, spleen and lungs.

In the sphenoid sinus, perforation occurs as follows:

(*a*) Through the floor or anterior wall of the sphenoid and into the superior pharynx. An abscess forms between the bone and the mucous membrane of the roof of the pharynx.

(*b*) Through the roof of the sphenoid in the general neighborhood of the sella turcica. This leads immediately to certain intracranial complications (extradural abscess at the base of the skull, meningitis, sinus thrombosis), which will be discussed subsequently. An illustrative postmortem report is that of Key-Alberg:[51]

Postmortem examination showed the following: meningitis in the ventricles and in the subarachnoid cavities at the base, especially in the posterior cavum cranii. There was no exudate over the hemispheres. After removal of the infundibulum, an irregularly shaped lesion the size of a farthing was found to the right of the anterior wall of the sella turcica. This perforation had blood-stained edges, and opened into the sphenoidal cavity, which still contained a not inconsiderable quantity of pus, mixed with blood and coagulation. Thrombosis was present in the cavernous sinus on both sides and in the ophthalmic vein on the right side.

The pathologico-anatomic possibilities and the difficulties in diagnosis and in interpretation of the postmortem findings are well illustrated by one of the cases from Mount Sinai Hospital, reported by Kramer:[47]

A woman, aged 53, had a prodromal period of one month in which there was headache, continued nasal discharge, intermittent vomiting, pain in the back of the

49. Hoston: Norsk. mag. f. lægevidensk. **72**:559, 1921.
50. Grant: Laryngoscope **41**:842, 1931.
51. Key-Alberg: Acta oto-laryng. **3**:37, 1921.

head, septic temperature for three days before admission, unconsciousness, and then coma. Death occurred twelve hours after admission.

Briefly summarized, postmortem examination showed pus in the left antrum and some of the ethmoid cells; the sphenoid sinus was absent. In the body of the sphenoid there was a sinus tract (possibility of craniopharyngeal sinus infection) 0.5 cm. in diameter, filled with detritus, which ran from the roof of the nasopharynx through the sphenoid bone in an upward and backward direction for a distance of 1.5 cm. The sella turcica was eroded, and the periosteum over the sphenoid bone at the base of the skull was considerably thickened, and in places it was lifted from the underlying bone. There were basilar meningitis, hypophysitis, ependymitis, purulent bronchopneumonia and an old tuberculous cavity.

The spread of an osteomyelitic process originating in the sphenoid occurs from the posterior part of the body of the sphenoid to the adjacent part of the basilar process of the occipital bone across the line of articulation. The physical basis for the extension in this direction and its limitation thereto lies in the occurrence of diploic tissue in this part of the sphenoid only, and in its continuation into the basilar portion of the occipital bone; diploic tissue is apparently absent in other parts of the sphenoid. Rarely, if ever, apparently, and for this reason, does the process extend outward into the wings of the sphenoid; I have seen no mention of this in the reported cases; in one case its absence is distinctly commented on (Grant [50]) in the postmortem protocol.

It is characteristic of osteomyelitis of the skull originating in the sphenoid that the process is always localized and is limited to the posterior part of the body of the sphenoid and the basilar portion of the occipital bone. Diffuse forms of osteomyelitis of the skull never occur from a sphenoid origin. The close proximity to the extremely important structures at the base of the brain, the great opportunity and facility for the transference of the infection to and within the meninges, the ease and readiness with which extradural abscess forms, all make for a rapid development of fatal intracranial lesions, which bring death before the osteomyelitis can spread to any great distance.

The symptomatology of cases of sphenoid perforation has certain characteristic features:

(*a*) Cases are reported by Eagleton [48] and others in which a tumefaction is palpated in the roof of the pharynx, which when opened is found to be referable to a perforation in the appropriate wall of the sphenoid. Undoubtedly this happens more often clinically and is not diagnosticated because practitioners do not often palpate the superior pharynx, and in any case the swellings are difficult to feel; spontaneous perforation then occurs. The latter is also commonly unrecognized owing to the fusion of the resultant discharge, after spontaneous perforation through the mucous membrane of the pharynx, with that from the natural opening of the sphenoid, from other sinus groups or from the general nasopharyngeal cavity.

(*b*) Occasionally the perforation is to one or the other side of the midline; suppuration then develops in the general neighborhood of the pterygomaxillary fossa. The latter conditions may be suspected, if, with distinguishable signs of sphenoid disease, difficulty and inhibition is present in the free use of the temporomaxillary articulation (opening of the jaws). Commonly this complication is unrecognized.

Except for a limited number of cases of this kind, it is not possible to distinguish any symptomatology inherently referable to any osteomyelitis at the base of the skull originating from the sphenoid, because the occurrence of the latter is invariably associated with intracranial complications, notably a basilar meningitis, the signs of which dominate the clinical picture. The diagnosis is to be made by inference only in the following circumstances:

(*c*) It seems correct to say that in cases of established or suspected sphenoid sinus disease, a sudden, acute, overwhelming exacerbation of symptoms, especially if these point to the basal meningeal areas, indicate a perforation in the roof of the sphenoid.

(*d*) A less dramatic and slower development of an intracranial lesion indicates the probable, though not the invariable, preexistence of an osteomyelitis. In general, it is to be said that in any patient with subjective and objective signs of sphenoid sinus disease, the occurrence of persistent headache and vomiting, and the development of the objective signs of meningeal irritation—stiffness of the neck, Kernig sign, etc.—should lead one to suspect that an intracranial lesion is developing, so that there is urgent need of immediate verification. Any more or less proved suspicion of the presence of an intracranial complication should immediately furnish the necessary criteria for the assumption that an osteomyelitis at the base of the skull originating in the sphenoid is probably present. The literature gives one the impression that neurologists have been more alert in making this diagnosis than the rhinologists.

Osteomyelitis of the sphenoid, because of the predilection for intracranial complications, especially purulent basilar meningitis, is apt to have (1) either a very acute and fulminant course with a fatality in a few days, or (2) a more chronic course lasting a month or more and ending most usually in death. Commonly the clinical course shows a combination of the two: a more or less prodromal period with obscure symptoms and physical signs, and then a sudden overwhelming of the body with fulminating infection, usually the expression of a terminal meningitis, which rapidly results in death.

A most important symptom in sphenoid sinus disease and in osteomyelitis of the base of the skull derived therefrom is pain in the head. Pain in the ear and mastoid regions occurring on both sides simultaneously in the absence of any objective signs of disease in those regions should lead one's attention to trouble at the base of the skull

in the region of the sphenoid. Even in the presence of disturbance in the mastoid regions, such pain has a certain amount of significance. Diffuse headache is also important. It sometimes begins in the frontal region and spreads to the occipital region; it then indicates involvement of the sphenoid region. When the headache becomes persistent and possibly of increasing severity, when it is difficult to control by the ordinary means and when it is associated with lethargy and, possibly with occasional vomiting, it becomes the most important single sign and symptom of the prodromal period in which osteomyelitis of the sphenoid bridges the chasm between sphenoid sinus disease and fatal intracranial complications.

Choked disk with optic neuritis is another important symptom of sphenoid disease. The discussion of this symptom beyond its bare mention is possibly beyond the scope of this paper.

## OSTEOMYELITIS OF THE SKULL IN ASSOCIATION WITH ACUTE INFECTION OF THE TONSILS

The importance of the intercurrence of an additional acute infection in a subject in whom a preexisting sinus disease is present—especially sphenoid sinus disease—as a factor in the exacerbation of the sinus disease which leads to the occurrence of intracranial complications was pointed out and emphasized by Eagleton.[48]

There are references in the literature to cases of acute osteomyelitis of the base of the skull that have followed an acute infection of the tonsils, or have followed an operation on the tonsils and adenoids. As there is always present an older lesion in the nasal accessory sinuses, most usually in the sphenoid cells, Eagleton assumed that the acute infection in the tonsils or that following the operation on the tonsils and adenoids has brought about an acute exacerbation of the infection in the sinuses, and that the osteomyelitis of the skull owes its existence to the latter. The assumption seems most reasonable and is probably correct.

I have been able to find the following illustrative cases in the literature:

Jacques and Lucien.[52]—A peritonsillar abscess was present, which was opened. The ears were normal. A gangrenous osteomyelitis of the body of the sphenoid and the apex of the petrous bone developed. A cavernous sinus thrombosis followed. Death occurred in three days.

Hoston.[49]—The symptoms started in the neck. There was pain when the patient opened his mouth. Death occurred in five days. Diagnosis on section was angina phlegmonosa, thrombosed cavernous sinus, osteomyelitis and necrosis of the sphenoid and occipital bones, purulent meningitis and edema of the meninges.

Wylie.[41]—In a 48 year old woman acute tonsillitis developed, followed by a peritonsillar abscess. In the following sixteen days there was increasing swelling

52. Jacques and Lucien: Bull. et mém. Soc. franç. d'otol., May, 1908.

and proptosis of the left eyeball and much pain in the throat and back of the head. The abscess was incised. Two days later, the temperature was still elevated, and thick pus was escaping from the wound. Both eyes became swollen. Death followed.

Postmortem examination showed a large sloughing abscess, lateral and posterior to the pharynx, extending upward to the base of the skull in the prevertebral area, to a focus in the basiocciput and sphenoid. Meningitis and encephalitis were also present.

O'MALLEY.[53]—Three weeks after an operation on the tonsils and adenoids signs of a cavernous sinus thrombosis appeared, and the patient died soon thereafter. Postmortem examination showed, in addition, osteomyelitis of the body of the sphenoid.

O'Malley's experience was that in all cases of death from cavernous sinus thrombosis following tonsillectomy, the sphenoid was involved.

D. Special Characteristics in Cases Associated with Antral Disease: A good deal of confusion exists between the subjects of antral infection and osteomyelitis of the superior maxilla. It seems undoubted that either one can produce the other. In any event, extension of infection from the superior maxilla into the cranial bones, no matter what the etiology is, seems to be extremely rare. Communication with the cranium exists at the nasal process of the maxilla or through its ethmoidal connections; and it seems very probable when antral sinusitis is followed by an osteomyelitis of the skull, that other sinus groups, notably the frontal and ethmoid groups, are also involved. The following are illustrative cases:

SKILLERN.[38]—This case is an example of an extension of an osteomyelitis of the nasal process of the superior maxilla to the frontal bone and skull. It appears that pansinusitis existed, and osteomyelitis developed in the maxilla and spread on the one side to the frontal bone and, on the other, to the malar bone. The infection was due to Staphylococcus aureus.

HANSON.[54]—There was a left upper "abscessed" tooth, which was extracted. Foul suppuration was found in the left antrum, which was drained by osteotomy of the nasal and facial surfaces at the anterior inferior angle in front of and below the inferior turbinate bone. There was a recurrence of symptoms, and extension of the process upward; an incision was made over the left frontal sinus, and the diseased bone exposed. Sequestrums were removed from the frontal bone. Bacteriologic examination showed Streptococcus hemolyticus. The patient was lethargic, with signs of meningeal irritation, convulsions and stupor; then death followed. Postmortem examination was not made.

CONNER.[55]—A 38 year old man had suppurative maxillary sinusitis; the other sinuses apparently were not involved; drainage was obtained through the socket of the second upper left bicuspid and by enlarging the opening in the inferior meatus. A small infected lesion was present in the floor of the vestibule of the

53. O'Malley, in discussion on Davis: Proc. Soc. Med. (Laryngol. Sect.) **13**:174, 1912.

54. Hanson: U. S. Vet. Bur. M. Bull. **6**:241 (March) 1930.

55. Conner, W. H.: U. S. Vet. Bur. M. Bull. **5**:417 (June) 1929.

left nostril. There was pain along the distribution of the left fifth nerve, and fever. A tender swelling developed in the region of the left lacrimal sac, increasing to cover the whole infra-orbital region. A roentgenogram showed no apparent involvement of the frontal sinus, but the swelling extended upward onto the forehead and to the opposite side of the nose. Incisions were made in the left cheek, the forehead and the right side of the nose; the periosteum was lifted; the bone was found inflamed, but there were no sequestrums. Bacteriologic examination showed streptococcus, Staphylococcus albus and Micrococcus catarrhalis. Culture of the blood gave negative results. There were signs of meningitis. The patient died.

The mechanism is apparently one of two: (1) extension of an osteomyelitic process in the maxilla through its nasal process into the frontal bone, or (2) as in other cases of frontal sinus disease, due to an associated frontal sinusitis.

The occurrence of osteomyelitis of the skull under either of these two conditions is rare.

*Extension from a Focus of Infection in the Otologic Apparatus.*—In discussing this phase of the subject of osteomyelitis of the skull, no attempt will be made to include the subject of middle ear or mastoid disease as customarily understood among internists and otologists, except where elucidation of the subject of cranial osteomyelitis demands it.

There is little in the literature concerning cranial osteomyelitis after middle ear and mastoid disease. This is encountered under two conditions: (1) as isolated and incomplete references to this association in the reports of cases of mastoid disease or (2) in larger communications dealing (*a*) with the subject of nasal accessory sinus disease and its complications, or (*b*) with the subject of cranial osteomyelitis. The sparsity of the literature is noteworthy because it calls attention to the actual small numbers of cases of cranial osteomyelitis that follow an otologic origin, and to the relative abundance of this complication after nasal accessory sinus disease as compared with its occurrence after middle ear and mastoid disease.

A report of 266 cases of streptococcic osteomyelitis of the temporal bone was made by Boyd-Snee[56] in 1922. A great many facts were given, out of which one can extricate the following: (1) It is always associated with a middle ear infection or with an exacerbation of it; (2) invasion occurs by continuity of structure or by hematogenous paths; (3) the streptococcus is always present; (4) the term used is "uncomplicated" osteomyelitis of the temporal bone, and (5) the mastoid is apparently uninvolved; (6) the symptomatology is that of mastoiditis; (7) the usual intracranial complications are likely to occur—thrombophlebitis, meningitis and brain abscess.

56. Boyd-Snee, H.: J. Indiana M. A. **15**:147 (May) 1922.

In the discussion of Boyd-Snee's paper (Breitenbach, Bulson), there was not entire agreement with the conclusions of Boyd-Snee. There seems to be a strong possibility that many cases of unusually widespread mastoiditis might have been included in the 266 cases reported by Boyd-Snee.

Osteomyelitis of the skull complicating middle ear and mastoid disease is far rarer than is the same complication after nasal accessory sinus disease. This is due both to (*a*) the essential anatomic conditions and (*b*) to the character of the manipulations during operation for mastoid disease.

(*a*) The squamous portion of the temporal bone, the petrous pyramid, the zygoma, the adjacent parietal bone, and the occipital bone are the bony structures that are of most interest. In looking at an articulated skull, it is readily seen that the pneumatic portion of the temporal bone, which makes up the mastoid, is surrounded in the superior, anterior and posterior directions by a continuous area in which the diploe between the tables of the skull is at a minimum. In the flare of the squamous portion of the temporal bone the diploe is absent; some diploe is usually present in the root of the zygoma; anteriorly, where the bone articulates with the wings of the sphenoid, it increases somewhat in extent; toward the occipital bone, the cancellous structure begins to become prominent. Here, however, it will be noted that the pneumatic structure of the mastoid is accomplished by plates of dense bone, and no true diploe exists. Posteriorly, also, where the temporal bone articulates with the occipital bone, the lateral sinus is lodged, and the diploe practically does not exist as its potential space is occupied by the venous sinus.

At the periphery of the temporal bone, where the bone thickens out to articulate with its neighbors, diploic structure begins to appear (fig. 8). In adults, as was pointed out previously, when the articulations disappear, the venous plexus contained in this diploic structure becomes continuous with that of its neighboring bones, the parietal, the occipital and the greater wing of the sphenoid.

The petrous portion of the temporal bone is composed of dense hard bone. It contains the auditory apparatus and the labyrinth and several canals for the transmission of nerves and vascular channels. In spite of its traditional hardness, a certain amount of cancellous (diploic) structure is found scattered in the very hard dense bone which makes up the bulk of the petrous pyramid and which makes up the various walls of the auditory apparatus, the labyrinth and of the various channels. Even though the middle ear and the mastoid cells are so closely associated with the pyramid, this dense bone seems to wall off the latter chambers very effectually from the little diploic structure contained within it.

Toward the base of the skull the apex of the pyramid lies in association with the basilar process of the occipital bone; the relationship resembles accurately that between the posterior part of the body of the sphenoid and the basiocciput.

In operating for mastoid disease, the aim is to clear out all of the pneumatic portion. When the operation is efficiently done, the entire cavity resulting from the operation is bounded by dense bone, and the latter is a fairly efficient barrier to the transfer of any infection into the cranial diploe.

In association with otologic infection, the spread of the latter occurs in a number of directions. According to Neumann,[57] they are, in order of their frequency: (1) mastoid process, (2) fossa sigmoidea, (3) tegmen tympani et antri, (4) petrosa, including the labyrinth and

Fig. 8.—Cross-section of a temporal bone to show the relationship and distribution of the cancellous and hard bone.

(5) posterior limb of the external semicircular canal and the carotid canal. According to Druss,[58] from whom I am taking these facts and who gives the experience at the Mount Sinai otologic (Friesner) service, while the predilection for the cells of the petrous pyramid is fourth on the list, nevertheless, a petrositis is far more prevalent than was previously believed. This has been demonstrated both clinically and histologically.

The foci of osteomyelitis which are found in the skull in association with otologic infection occur, roughly, at the following sites:

(1) In the occipital bone. This is the commonest form, as when the infection spreads backward from the mastoid into the contiguous part of the occipital bone. It is usually interpreted as being an

57. Neumann, Heinrich: Die otitische Kleinhirn-Abscess, Vienna, Franz Deuticke, 1907.

58. Druss, J. G.: Laryngoscope **41**:394 (June) 1931.

extraordinary extension of the mastoid cells, but in a certain number of these it is undoubted that there is a true extension into the diploe of the occipital bone. On the other hand, occipital involvement is extremely rare when a focus in the petrous pyramid spreads by contiguity to the basiocciput; this will be discussed subsequently in the section devoted to osteomyelitis in the pyramid.

(2) In the zygoma. This is possibly next in frequency, and is usually found at the root and in the body of the zygoma; it is also sometimes interpreted as being an extraordinary development of the mastoid cellular structure. The lesion tends to localize itself in a relatively small area, and being very close to the floor of the middle fossa, it is one of the varieties in which perforation is found to occur into the interior of the cranium and to give rise to extradural abscess and meningitis. Such a case was reported by Druss and Friesner [59] from Friesner's service at Mount Sinai Hospital:

A boy, 6 years old, had headache, pain in the left ear and spontaneous rupture of the drum. The symptoms continued. There were physical signs of meningitis. The spinal fluid contained meningococcus, and a blood culture was sterile. A roentgenogram of the mastoid area was negative. The boy was discharged with a diagnosis of meningococcus meningitis.

He was readmitted five months later with a seventeen day history of aural discharge, for which myringotomy was done. Twelve hours before admission, there were frontal headache and vomiting. The spinal fluid showed gram-positive cocci, which did not grow on culture. There was an increase in symptoms. Focal neurologic symptoms led to a diagnosis of temporosphenoidal abscess. The patient died.

Postmortem examination showed osteomyelitis of the inner aspect of the zygoma in the temporal bone and perforation of the bone through the adherent meninges. The remainder of the temporal bone was normal. There was a temporal lobe abscess.

(3) In the squama. The thinness of bone in this locality is proverbial, and various forms of subdural abscess and meningitis are described. An illustrative case is reported by Eagleton: [48]

The patient suffered from a deficiency in hearing. Sore throat developed, followed by increased diminution of hearing. Paracentesis was done to relieve the pain. The maxillary antrum was drained. After a right mastoidotomy the patient did well.

"Cold" developed, followed by pain on the top of the head. The mastoid wound suppurated. There were no meningeal symptoms; lumbar puncture revealed a sterile fluid. Operation showed extensive superficial necrosis of the squama just above the external auditory canal and zygoma, caries in the solid angle and serous meningitis. The sinus was free from disease.

Sepsis continued. Blood culture showed long chain streptococcus. The focus was found to be in the shoulder. Death occurred.

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59. Druss, J. G., and Friesner, I.: Pathways of Infection in Abscess of the Brain, Arch. Otolaryng. **13**:532 (April) 1931.

Postmortem examination showed thrombophlebitis of the right jugular vein and bulb, a carious condition of the base of the skull over the sphenoid extending into the basilar process of the occipital bone, serous meningitis with areas of exudation, pneumonia and pericarditis.

(4) In the petrous pyramid. Druss [58] studied these cases at Mount Sinai Hospital. Various paths have been described by Perkins,[60] Sears,[61] Chamberlain,[62] Maybaum [63] and others for the routes of extension of the infection from the middle ear and antrum to the pyramid. In the

Fig. 9.—Low power picture from Druss' case showing at *A* the location of the abscess in the root of the zygoma. (Courtesy of Dr. Druss.)

main, they are along the paralabyrinthine cells (above, below and on the side of the labyrinth), along the cells accompanying the eustachian tube, through the carotid canal, through the subarcuate fossa, along the superior and inferior petrosal veins, from an extension of an extradural abscess or from a combination of these. As it spreads through the petrous

60. Perkins: Ann. Otol. **19**:692, 1910.
61. Sears: Pennsylvania M. J. **3**:844, 1910.
62. Chamberlain: M. J. **27**:566, 1924.
63. Maybaum, J. L.: Laryngoscope **30**:138, 1920.

pyramid, the infection may involve or avoid the labyrinth in its course. Other factors being equal, the more cellular the petrous pyramid, the more ideal is the situation for the spread of infection.

According to Druss,[58] the mastoid process, the petrous pyramid and the apex differ in their anatomic structure and in their pathologic picture. Usually the degree of infection is greater in the mastoid cells than in the paralabyrinthine cells, but the contrary may be true, and there may be little or no infection in the mastoid cells, and the paralabyrinthine cells or the cells at the apex may be the seat of a localized collection of pus. Such cases have been reported by Otto Mayer, Karlefore, Ulrich (quoted by Belinoff and Balan[64]) and others. Druss[58] demonstrated histologically that infection may subside in the middle ear and mastoid cavity but will increase in severity as it advances through the petrous pyramid. This bears out clinically the not too frequent occurrence of a dry, resolving middle ear associated with an intracranial complication.

These anatomic considerations give the physical basis (1) for the occurrence of osteomyelitis of the skull as a complication of middle ear and mastoid disease, (2) for its relative sparsity of numbers as compared with similar complications after nasal accessory sinus disease, (3) for the essential similarity of the clinical symptom complex and course and for similar associations with similar groups of intracranial complications.

The anatomic considerations outlined here give the physical basis for the very much lessened likelihood, which exists in otologic conditions necessitating mastoidectomy, of direct infection of the cranial diploe during the manipulations and steps of the operation. Unless the diploe is unusually well developed and extends well into and toward the field of a mastoid operation, it is difficult to understand how direct infection could mechanically be implanted into the diploe.

The following types of lesions are found:

(1) Perforations. These are unusual. The cases at Mount Sinai Hospital included only one of these in which the perforation occurred in the neighborhood of the root of the zygoma. Theoretically, perforations ought to be found with disease in the squama.

(2) Localized lesions. These form the bulk of the lesions found. Their localizations and physical appearances have been sufficiently indicated in the previous paragraphs. Practically all the remarks made here concern the localized type of disease.

(3) Diffuse lesions. There are no cases of this kind in the records at Mount Sinai. When I speak to otologists about this type of lesion, every one is of the belief that they are very rare; and no one, when

64. Belinoff and Balan: Monatschr. f. Ohrenh. **64**:1185, 1930.

actually pressed for an example, can give me a specific instance of this kind. I have a slight recollection of having seen mention of such an experience in the literature, but I am unable to remember where and under what condition. I get the distinct impression that diffuse cases of osteomyelitis of the skull are extremely uncommon after otologic and mastoid disease.

The sequence of events, when the osteomyelitis of the skull has an otologic origin, is, for practical purposes, exactly similar to that complicating nasal accessory sinus disease. Both of these sets of organs are hollow chambers, either of a simple or of a complicated outline, lined by mucous membrane and subject to the same type of infection produced in similar ways; indeed, in many cases there is a "pansinusitis," all of the accessory structures that communicate with the nasopharynx being included in this term. The bacteriology is similar; the essential pathology is similar, and the mechanism of production and the progression of the lesion is similar.

The relative sparsity of cases of cranial osteomyelitis after an otologic origin is explained by the relatively efficient way in which the area of primary infection—middle ear and mastoid—is walled off from connection with the general cranial diploe and with the relative sparsity of diploe which exists in that part of the skull immediately adjacent to the primary area. Probably in those cases in which the osteomyelitis of the skull develops, the diploe is extraordinarily well developed and reaches downward toward the area of primary infection to a greater extent than is usual. Given a similar origin, with similar organisms and similar pathogenesis and pathologico-anatomic lesions, it is to be expected that the clinical course will be similar in both types of cases—in those with origins in the nasal accessory sinuses and in the otologic area. For this very good reason, no attempt will be made to describe these aspects of the subject, as it will only necessitate repeating what was said in the part of this communication dealing with cases of osteomyelitis of the skull after nasal accessory sinus disease.

Exactly similar considerations apply with equal force to the various intracranial complications that occur—to their variety, to their pathogenesis, to their clinical course, to their treatment and to the final outcome.

Frey [65] has attempted to differentiate cases of ordinary middle ear and mastoid disease from cases of osteomyelitis of the temporal bone unassociated with otologic infection. His differential diagnosis depends on the following criteria: (1) particularly rapid development of the manifestations; (2) rapid deterioration of the general condition from the beginning with high temperatures, prostration, anorexia and rest-

65. Frey, G.: J. Laryng. & Otol. **40**:308 (May) 1925.

lessness; (3) the presence of a retro-auricular swelling with especial reference to its early appearance, size and its tendency to extend rapidly beyond the mastoid limits; (4) the virulence of the infection; (5) frequency of involvement of the facial nerve and of disturbances of the vestibular apparatus; (6) the operative appearances: (*a*) the tendency to necrosis, (*b*) the presence of foci close by in the zygoma, squama or pyramid, or at a distance by way of the diploic veins; (7) rapid progress of the disease, and (8) involvement of other than the lateral sinus. Frey cited the following case:

A boy, aged 4 years, had a retro-auricular swelling behind and below the mastoid and extending to the occiput and into the muscles of the neck. At operation there was widespread necrosis, and the osteitis was found to extend into the spongy cancellous tissue of the zygoma and the occipital bone. A thrombosis of the lateral sinus with a surrounding abscess was present also.

Four days after operation, there was present chemosis of the upper eyelids and exophthalmos; the temperature was 105 F. The spinal fluid was negative; blood culture was sterile, and bacteriologic examination of the pus showed staphylococcus. Eight days later jaundice developed, and death occurred.

I have no doubt that cases of osteomyelitis of the temporal bone of this type—and most probably they are of hematogenous origin—occur from time to time. The chances are good that these differentiating criteria which Frey proposes are sound, and they are confirmed by Wittmack;[66] but it would take exceptionally sound and clever clinical sense to make the differentiation unless evidence of a hematogenous infection in general is undoubted and beyond question. One of the points that would carry weight with me would be the presence of Staphylococcus aureus as the provocative and etiologic organism for the infection.

A group of cases occur in which a focus develops in the petrous portion of the temporal bone and in which there is either no evidence of preceding middle ear disease or of mastoid involvement, or in which the middle ear alone is involved; sometimes the middle ear manifestations appear some time after the evidences of pyramid disease. In these cases the discussion always centers around the question of hematogenous infection. My own impression is that many of these are of hematogenous origin. There have been several such instances in the otologic service at the hospital, but usually the available data is somewhat insufficient to enable one to make an incontrovertible opinion. A pertinent case is the following:

A 62 year old colored man entered the hospital (service of Dr. Baehr and Dr. Freisner) with an unimportant history except for occasional gas pains during

66. Wittmaack, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926.

the past three or four years. His present illness began four weeks before admission with an initial shaking chill followed by attacks of pain in the lower aspect of the left side of the chest, not increased by respiration, and accompanied by continued high temperature and daily severe chills. Physical examination revealed an acutely ill man with some impaired mobility of the left leaf of the diaphragm, bilateral costovertebral tenderness, more marked on the right, and marked tenderness over the liver. Blood pressure was 130 systolic and 90 diastolic. Hemoglobin was 82 per cent, the white blood count, 22,000 with 86 per cent polymorphonuclears. The Pirquet test was positive.

This clinical course continued in the hospital, and a week after admission a complete exploratory laparotomy was done, but nothing abnormal was found. The wound healed by primary union.

The course continued septic. The Wassermann test was negative. Blood cultures were persistently negative. Agglutination tests for typhoid and melitensis were negative. A search for malarial parasites revealed nothing. Prostatic smear revealed some pus cells but no organisms. Roentgenograms of the chest on two occasions were negative. Roentgen examination of the stomach and duodenum gave negative results. Normal urine persisted throughout the patient's stay in the hospital, and an intravenous pyelogram, taken to rule out some kidney infection such as a carbuncle, also revealed nothing. A leukocytosis of from 20,000 to 30,000 white cells with a polynucleosis of 90 per cent persisted. The general condition of the patient gradually deteriorated, and the only physical sign obtainable after operation was persistent marked tenderness over the liver.

Three weeks after admission, aspiration of the liver was performed. No organisms were obtained, and culture was negative. On the same day, following the aspiration, the patient had a severe shaking chill and a rise in temperature to 104 F. Examination shortly thereafter revealed definite signs of meningeal irritation; a spinal tap was performed, cloudy fluid being obtained that contained 4,000 cells and 76 per cent polymorphonuclear cells; smear and culture of the latter were negative. Daily examination of both ears revealed no changes. The sepsis and the meningeal signs remained unchanged, and the spinal fluid gradually improved; about eight days later the latter was clear and contained only 12 cells. The next day a thick discharge developed from the right ear; the ear drum was flat anteriorly, and only a small amount of fairly thick discharge was present in the inferior sulcus; smear and culture of this pus revealed a pneumococcus type III. A roentgenogram of the mastoids was negative.

Two days after the ear began to discharge, a spinal tap was again taken and revealed a cloudy fluid with 2,500 cells, 78 per cent of which were polymorphonuclear cells. A terminal bronchopneumonia preceded death about forty-eight hours later.

Postmortem examination revealed: chronic purulent osteomyelitis of the petrous portion of the temporal bone (right) with bone abscess, acute purulent basilar meningitis, carbuncle of the left suprarenal with suppuration of the posterior wall of the lesser sac and phlebitis of the splenic vein, thrombophlebitis of the portal vein with phlegmonous suppuration of the liver, bronchopneumonia of both lower lobes of the lungs, acute purulent bronchitis, parenchymatous degeneration of the viscera, acute congestion of the lungs and the liver, atherosclerosis with calcification of the aorta, hypertrophy of the left ventricle of the heart, and cysts of the kidneys.

The notes of the case are deficient in very valuable and pertinent bacteriologic data. Nevertheless, it seems evident that this entire

clinical entity is a hematogenous general infection with undemonstrable bacteremia in which metastatic foci were present in the suprarenal gland (a carbuncle) and in the petrous portion of the temporal bone. This opinion is concurred in by the otologic department at Mount Sinai Hospital (Friesner), and by the medical department (Dr. Baehr).

There is a marked clinical similarity between disease of the pyramid and of the sphenoid bone. Both of these lie in the same anatomic position with reference to the base of the skull and the adjoining intracranial structures. Perforations occur in the pyramid as well as in the sphenoid, and there is the same predilection for extradural abscess and meningitis; brain abscess also occurs. A characteristic symptom complex for pyramid disease is Gradenigo's syndrome—involvement of the gasserian ganglion and of the abducent nerve; but as the syndrome has been found to occur without bone change, the connection is not absolute.

The intimate associations between the petrous pyramid and the sphenoid bone is well illustrated in the case reported by Gelanze:[67]

> In this patient there was a ten years' history of a chronic otorrhea and chronic otitis media which followed an influenza. The present recrudescence began two months before admission with pain, fever, increased discharge, considerable retroauricular swelling and the physical signs of meningitis, including turbid lumbar fluid. A mastoid operation was done, and following this the manifestations diminished.
>
> One week before death the symptoms reappeared with increased meningeal signs. The local mastoid wound and the middle ear were not in satisfactory shape (fungous granulations, cholesteatomas), and there was necrotic and sequestrating bone. The symptoms increased, and facial paralysis developed. There was a sudden aggravation of symptoms followed by death.
>
> The postmortem anatomic diagnosis was seropurulent meningitis of the left temporal and cerebellar fossa; necrosis of the petrous bone, the sphenoid bone and the sella turcica, with perihypophysitis.

On careful study of this case, I agree with Gelanze[67] that the infectious process, produced by germs of considerable virulence with a marked necrotizing power, had in the first place attacked the meninges through the tegmen antri, giving rise to meningitis which was promptly circumscribed by the local reaction. In spite of the rather extensive mastoid evacuation at the first operation, the osteomyelitic process became promptly propagated to the perilabyrinthine cells and to the labyrinth itself, thus permitting the germs again to attack the cerebellar fossa by way of the saccus endolymphaticus and to give rise to a new meningitic process. At the same time, in spite of the second intervention, and the complete petrotympanic evacuation, the necrotizing osteomyelitic process rapidly advanced toward the petrous bone and after only two days resulted in sequestration of the entire facial segment,

67. Gelanze, C.: Valsalva **6**:86, 1930.

followed by paralysis of the facial nerve; the entire acoustico-vestibular nerve bundles underwent necrosis. On reaching the extreme mesial limit of the petrous bone, the osteomyelitis by way of the periosteal vessels and lymphatics next attacked the body of the sphenoid bone and became diffused to the sella turcica, giving rise by its vicinity to a perihypophysitis which remained without evident clinical symptoms. The extension of the necrotic process and the considerable absorption of the toxic substances produced in large amounts in the infectious focus were the principal causes of the patient's death.

I have been able to find the following additional cases of osteomyelitis of the skull of otologic origin reported by various authors in the literature:

HUNTER TODD.[68]—A 53 year old woman had middle ear and mastoid disease; during mastoidectomy, an area of osteomyelitis was exposed behind the mastoid extending into the occipital bone as large as the palm of one's hand. There was secondary spontaneous sequestration of necrotic bone from the occipital area. Later recrudescence of symptoms occurred over the parietal bone with operative revision of the wounds and new areas. There was a period of partial remission with recrudescence of symptoms. The patient's condition followed a gradual downward course until death. Postmortem examination showed the typical wormeaten appearance of the cranial bones with areas where the bone was absent (sequestrated areas).

HARRISON.[69]—A 25 year old man had middle ear and mastoid disease; radical mastoidectomy was followed by septic type of temperature. On revision of the wound thrombophlebitis of the lateral sinus was found. The symptoms continued. There were subperiosteal abscess over the squamous portion of the temporal bone, spontaneous sequestration and numerous abscesses under the scalp. The patient was operated on twenty times, with recovery.

GRUNWALD.[70]—A 63 year old man had middle ear and mastoid disease; at mastoidectomy, no pus was found, but the cells contained granulations. Later, an abscess in the posterior triangle of the neck was incised and drained. There was retention of pus. On revision bare bone was felt in the occipital region. Secondary revision was done with removal of the occipital bone as far as the inferior nuchal line, the seat of a necrotizing osteomyelitis.

PRATT.[71]—A boy of 5 years had a purulent middle ear disease; the mastoid was explored because of stiffness of the neck and a turbid spinal fluid containing hemolytic streptococci. Revision was done because the patient's condition did not improve. The intracranial contents were explored at this time with negative results. The patient died. Postmortem examination showed necrosis of the anterosuperior part of the petrous pyramid, and meningitis.

EAGLETON.[48]—The patient suffered from alcoholic periodic insanity. There was infection of the upper respiratory tract with severe pain in the head; on the following day a stiff neck and pain in both ears developed. There was bogginess

68. Todd, quoted by Luc (footnote 5).

69. Harrison: J. Laryng., Rhin. & Otol. **27**:628, 1912.

70. Grunwald: Ztschr. f. Hals-, Nasen- u. Ohrenh. **2**:139, 1922.

71. Pratt, E. L.: Laryngoscope **38**:409 (June) 1928.

over the mastoids. The patient had a high temperature, a cough, and was delirious and irrational. Two blood cultures were negative. Aural culture showed diplococcus. The right mastoid was explored, showing an abscess in the suboccipital region from suppurative osteomyelitis of the occipital bone and pus in the right mastoid. An antemortem blood culture (four hours) revealed streptococcus. Death occurred.

Postmortem examination showed: suppuration of the sphenoid sinus; occipital edema; superficial abscess below the mastoid; deep abscess in relation to the upper four cervical vertebrae; purulent thrombophlebitis of the right lateral sinus extending to the torcular and into the jugular veins, involving the right superior and inferior petrosal, cavernous and anterior and posterior circular veins. The left cavernous sinus and the superior longitudinal sinus were also involved. Other findings were incidental to the general infection in the viscera.

EAGLETON.[48]—The patient had a left chronic otitis media with acute exacerbation, accompanied with chills and fever (107 F.). Mastoidectomy revealed sclerosed bone and thrombophlebitis of the lateral sinus. Blood culture was negative. The septic type of temperature continued followed by operation on the jugular bulb (Grunert's operation); there was no bleeding from the inferior petrosal sinus. A blood transfusion was done. A second blood culture was negative. Lumbar puncture revealed the fluid under slight pressure, with a cell count of 28; the globulin was slightly increased; Fehling's solution was reduced. No organisms were present. The symptoms continued, and death occurred.

Postmortem examination showed marked jaundice, a small extradural abscess of the posterior surface of the left petrous bone, with a local area of necrosis near the posterior semicircular canal, the dura being separated from the bone; a suppurating jugular bulb and pus in the left lateral sinus extending to the torcular vein; thrombosis of the left superior and inferior petrosal veins; right cavernous sinus thrombosis, and thrombosis of the basilar plexus and anterior spinal veins passing through the foramen magnum.

## ROENTGENOGRAPHIC EVIDENCE IN OSTEOMYELITIS OF THE SKULL

Roentgenographic evidence of osteomyelitis of the skull, when once the lesion is established, is generally similar for all classes and varieties of cases no matter what the etiology or pathogenesis. This, as is generally true in all cases of osteomyelitis, is not available at the beginning of the development of the lesion but appears relatively late. The evidence is available under two conditions:

(1). In localized forms of disease. This is especially well demonstrable in the osteomyelitis that accompanies frontal sinus disease, and takes the form of well demarcated sequestrations.

(2). In the diffuse variety. There is a characteristic motheaten appearance of the bones of the skull.

Roentgenographic evidence is especially demonstrable and available with lesions in the vault. Lesions at the base of the skull, no matter what their roentgenographic morphology may be, are not demonstrable at all or are demonstrable with extreme difficulty; for this reason well demarcated lesions which occasionally occur in the ethmoid are not recognizable.

Associated and indirect roentgenographic evidence of osteomyelitis of the skull is available only in the class of lesion associated with nasal accessory sinus disease, and is produced by the sinusitis per se.

According to Pfahler,[72] the roentgenologic signs of deep perisinusitis or changes incident to chronic ethmoid-sphenoid sinusitis consist in a cloudiness with a vague shading off of the anatomic details, thickening of the posterior and lateral wall of the sphenoid and ethmoid sinuses and an area of increased density which indicates osteitis of the surrounding bone.

This perisinusitis commonly extends into the middle fossa of the skull, but may involve also the petrous and mastoid portions of the temporal bones and even the posterior fossa. In some cases it is general and involves the base of the skull, but in others is confined to the side in which there is a deep sinusitis. Therefore, the conclusion may be drawn that it is an extension of the inflammation directly from the affected sinus. Pfahler [72] suggests that an effect on the sella turcica resulting from an extension of the inflammatory process may account for unexplained anomalies that have been observed by roentgenologists for many years.

## OCCURRENCE OF GENERAL INFECTION IN OSTEOMYELITIS OF THE SKULL

Cases with clinical signs of a general infection can be found in each of the pathologic and clinical groups outlined in this paper as follows:

(*a*) As the original general infection to which the skull lesion is a metastatic lesion.

(*b*) As a result of a primary infection of the bone tissue of the skull in civil or military injuries.

(*c*) As a secondary phenomenon in extension cases of osteomyelitis of the skull.

(*d*) Accompanying intracranial complications, especially meningitis and sinus thrombosis.

The number of cases in which positive blood cultivations are obtained are relatively few considering the total number of cases of osteomyelitis of the skull that have occurred, but are relatively large when intracranial complications are present. Even in these cases, however, the numbers of positive blood cultivations are not as numerous as one might suppose, and in the cases from Mount Sinai Hospital a positive blood culture was secured in one case only.

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72. **Pfahler, G. E.:** Roentgenologic Signs Which Indicate Extension of Infection from the Ethmoid and Sphenoid Sinuses to the Base of the Skull, Arch. Otolaryng. **8**:638 (Dec.) 1928.

On the other hand, the numbers of cases in which there are undoubted clinical evidences of a general infection of the body, but in which the blood cultivations remain sterile, are relatively large, both in uncomplicated and in complicated osteomyelitis of the skull. Fatalities are very common in this group both because of the progressive nature of the local lesion and the occurrence of intracranial complications, as a consequence of the devastating effects of both of these two elements, and because of the general infection as evidenced by distant metastases.

## COMPLICATIONS

In cases of general blood infection (sepsis, septicemia, etc.), metastatic lesions are found post mortem in the various organs of the body; they are especially common in the kidneys, the liver and the lungs. I have encountered no mention of an endocardial lesion in cases of general infection of this kind (i. e., cranial osteomyelitis) in the literature. As was mentioned previously, the relatively uncommon occurrence of a general infection makes the finding of such metastatic lesions an equally infrequent one in clinical practice. Metastatic lesions such as these (i. e., in the kidney, liver, lungs) give no dominating picture and are commonly lost in the general symptomatology, both subjective and objective, of the clinical picture.

Cases of osteomyelitis of the skull, no matter what the provocative etiology is, are likely to be complicated by similar conditions, once they are fully developed; this is especially true when the infection has reached into the diploic venous system. Localized abscess formation is a relatively common complication.

### TYPES OF ABSCESSES AND COMPLICATIONS

*Single or Multiple Abscess.*—These abscesses are subperiosteal (subepicranial). At first confined below the epicranium, they quickly cause a dissolution of this membrane, after which they spread in the subcutaneous tissues of the scalp. In cases of multiple abscess there may be appreciable separating distances between the various localizations.

This variety of abscess is relatively uncommon in traumatic primary cases of osteomyelitis of the skull. It is very common in hematogenous cases and in extension cases derived from disease of the nasal accessory sinus; it is less common in ethmoid sinus disease and otologic cases, and does not occur in cases of cranial osteomyelitis derived from sphenoid sinus disease.

*Extradural Abscess.*—This abscess is the intracranial counterpart of the external abscess just described. It, too, is a subperiosteal abscess situated between the dura and the internal table of the skull. Its more complete discussion is reserved for the section devoted to intracranial complications.

In the individual clinical and pathologico-anatomic groupings outlined in this communication, other forms of localized abscess formation appear. They are as follows:

*Orbital Abscess and Phlegmon.*—These abscesses are apparently more common than the intracranial complications which they frequently precede. There seems little doubt that the majority of intra-orbital inflammatory conditions owe their origin to nasal accessory sinus disease, and in most of these the essential intervening link is osteomyelitis. The complication occurs most commonly in diseases of the ethmoid and the frontal sinuses as a direct complication, and in roundabout ways (i. e., by way of a thrombophlebitis in the vascular channels, especially in the ophthalmic veins) in cases of sphenoid sinus disease. Orbital abscess does not occur in the otologic cases.

Birch-Hirschfeld's [73] experience is that 60 per cent of orbital inflammatory conditions are due to nasal accessory sinus disease. Kuhnt thinks this percentage is too low.

The mechanism is as follows:

(*a*) By perforation through the bony wall. This is especially common in diseases of the frontal and ethmoid sinuses.

(*b*) By direct extension of the process through some natural opening—optic foramen, superior orbital fissure, etc.

The autopsy on a patient of Leegaards [74] showed pus in the sphenoidal sinus, in the orbit, around the first branch of the trigeminal and around the chiasm.

(*c*) By thrombosis of the ophthalmic veins. An illustrative case is the following:

The autopsy in Vail's [75] case showed: chronic sphenoidal suppuration (right), necrosis of the orbital wall of the sphenoid, orbital phlegmon and suppurative phlebitis of the ophthalmic vein, the cavernous sinus, etc.

Additional forms of localized abscess formation occur in the cases of osteomyelitis derived from sphenoid sinus disease.

*Abscess in the Roof of the Nasopharynx.*—This abscess is a variety of, and a frequent predecessor of, frank retropharyngeal abscess. As pointed out previously, this can be palpated in the roof and in the posterior wall of the nasopharynx.

*Abscess in the Pterygomaxillary Fossa.*—These abscesses most commonly develop as a result of suppurative conditions in the base of the skull associated with sphenoidal disease, and are usually associated with

73. Birch-Hirschfeld, A.: Vers. deutsch Naturf. u. Aerzte **9**:17, 1908.
74. Leegaards: Acta oto-laryng. **1**:343, 1918.
75. Vail: Laryngoscope **29**:263, 1919.

thrombophlebitis of the veins coming from the cavernous sinus and passing into the superior nasopharynx.

*Abscess in the Stylomaxillary Fossa.*—This abscess is a subvariety of pterygomaxillary abscess, and is especially common in those cases of sphenoid sinus disease in which a tonsillitis or a tonsillectomy has precipitated the clinical picture. The path of infection lies in the venous plexus of the carotid canal. The abscess may point in the neck below the angle of the jaw.

*Subperiosteal Abscess in the General Region of the Superior Aspect of the Spheno-Basiocciput.*—This type is specifically mentioned as a variety of extradural abscess which occurs with osteomyelitis of the skull derived almost exclusively from sphenoid sinus disease, and in relatively rare instances from an osteomyelitis of the apex of the petrous pyramid. It is the intervening link between bone disease in these localities and other intracranial complications (meningitis, venous sinus thrombosis, etc.), which will be discussed subsequently.

*Intracranial Complications.*—Osteomyelitis of the skull is especially noted for the occurrence of intracranial complications. In the twenty-nine cases of osteomyelitis of the skull compiled by Gerber, there developed:

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|---|---|
| Pachymeningitis | 4 times |
| Extradural abscess | 11 times |
| Intradural abscess | 1 time |
| Thrombophlebitis | 5 times |
| Cerebral abscess | 4 times |
| Meningitis | 9 times |
| Meningo-encephalitis (one septic) | 3 times |

In 1895, Kuhnt,[76] in his work on the frontal sinus, collected seventeen cases of intracranial complication associated with suppuration in that cavity. In twelve of these the frontal sinus only was diseased, while in the remaining five there was associated suppuration in other accessory cavities. Dreyfuss, in his monograph published in 1896, reported nineteen cases of a like nature following frontal sinus suppuration. The latter, however, are not to be regarded as being all additional to those reported by Kuhnt.[76] Killian, in his article on the frontal sinus in Heymann's "Handbuch der Laryngologie," published in 1900, brings the total number of frontal sinus complications up to thirty. Since that date, Turner has been able to add twelve additional cases not included in the statistics of the aforementioned writers, making the total number forty-two.

76. Kuhnt, Herman: Ueber die entzündlichen Erkrankungen der Stirnhöhlen, Wiesbaden, J. F. Bergmann, 1895.

According to Turner,[36] the postmortem evidence of intracranial infection is somewhat meager. Newton Pitt,[77] who gives an analysis of 9,000 autopsies, found only one case of cerebral abscess due to nasal suppuration; the patient had had nasal polypi and ethmoid disease. Gowers[78] considers that chronic nasal disease is an occasional but rare cause of cerebral abscess. He stated that in 240 instances of brain abscess, the nose was the primary seat of infection in six, but the sinuses implicated are not specified. Treitel[79] found in 6,000 postmortem examinations three cases in which the intracranial mischief had its origin in the nose, namely, two of cerebral abscess and one with purulent meningitis. Wertheim[39] had access to the records of 10,394 autopsies; among these were 127 cases of endocranial suppuration. Fourteen were stated to be of nasal origin, but in six only was the exact mode of infection specified. In only three of these, again, was the frontal sinus the probable primary source of the complication.

This was the status in 1905, when Turner[36] published his paper. Since then a good many observations have been published, and the experiences of men like Eagleton have been particularly valuable. As a matter of fact, most of these observations are published because of the intracranial complications, and a considerable literature dealing with the latter has grown. One obtains the impression that intracranial complications occur most commonly with osteomyelitis of the skull derived from sphenoid sinus disease; the same situation exists with cases of osteomyelitis in the petrous pyramid, except for the great rarity of cases arising from this source. As a matter of fact, one might almost say that osteomyelitis of the spheno-basiocciput or of the petrous pyramid is so anatomically situated as to almost compel, if not invite, intracranial complications. Cases derived from foci of infection in the frontal or ethmoid groups of nasal accessory sinuses do not so readily lend themselves to the occurrence of intracranial complications; this is also due to anatomic considerations associated with the vault of the skull as opposed to the more intimate relationships at the base; but even here, when once the slowness of development, characteristic of many of the cases of cranial osteomyelitis derived from the frontal and ethmoid groups of sinuses, is lost, and the rapidly developing diffuse form of osteomyelitis is present, disparity of any kind between these two clinical groups disappears.

There are some differences of opinion as to the relative frequency with which intracranial complications occur in the group of cases of osteomyelitis of the skull associated with nasal accessory sinus disease

77. Pitt, Newton: Brit. M. J. **1**:643, 1930.

78. Gowers, W. R.: A Manual of Diseases of the Nervous System, ed. 2, London, J. & A. Churchill, 1892.

79. Treitel, L.: Berl. klin. Wchnschr., 1896, no. 51.

I think that some confusion exists in that it is not clearly stated whether the individual opinions refer to "nasal accessory disease" or to the "cranial osteomyelitis" which complicates the latter. I am inclined to agree with Burger that the majority of endocranial complications after nasal accessory sinus disease occur through the mediation of an osteitis of the bones housing the sinuses and of their continuations into the neighboring flat cranial bones. According to Burger,[28] this is based on operative and autopsy experience. Dreyfuss [80] found this status in twelve of nineteen cases in relation to the frontal sinus. Gerber [26] is very outspoken in his belief that almost every endocranial complication has its origin in infection of the bony wall.

Mechanism of Development: The mechanism for the development of the intracranial complications of osteomyelitis of the skull is almost purely a vascular one, and the infection is transmitted along the venous channels.

There are two main vascular channels.

(*a*) The transmission of the infection occurs through the anastomoses between the veins of the diploe and the veins of the dura. According to Gray:

> These vessels communicate, in the interior of the cranium, with the meningeal veins and with the sinuses of the dura mater, and on the exterior of the skull with the veins of the pericranium and of the scalp. They are divided into the frontal, which opens into the supra-orbital vein by an aperture in the supra-orbital notch; the anterior temporal, which is confined chiefly to the frontal bone, and opens into one of the deep temporal veins, after escaping by an aperture in the great wing of the sphenoid; the posterior temporal, which is confined to the parietal bone, and terminates in the lateral sinus by an aperture at the posterior inferior angle of the parietal bone; and the occipital, the largest of the four, which is confined to the occipital bone, and opens either into the occipital vein or internally into the lateral sinus or torcular Herophili.

(*b*) By way of the emissary veins. According to Gray:

> The emissary veins are vessels which pass through apertures in the cranial wall and establish communications between the sinuses inside the skull and the veins external to it. Some of these are always present, others only occasionally so. They vary much in size in different individuals. The principal emissary veins are the following: (*a*) A vein, almost always present which passes through the mastoid foramen and connects the lateral sinus with the posterior auricular or with an occipital vein. (*b*) A vein which passes through the parietal foramen and connects the superior longitudinal sinus with the veins of the scalp. (*c*) A plexus of minute veins which pass through the anterior condyloid foramen and connect the occipital sinus with the vertebral vein and deep veins of the neck. (*d*) An inconstant vein which passes through the posterior condyloid foramen and connects the lateral sinus with the deep veins of the neck. (*e*) One or two

80. Dreyfuss: Sammelreferat, Ztschr. f. Ohrenh., 1908, vol. 103; quoted by Turner: Edinburgh M. J. **17**:231, 1905.

small veins which pass through the foramen lacerum medium and connect the cavernous sinus with the pterygoid and pharyngeal plexuses. (*f*) Two or three small veins which pass through the foramen lacerum medicum and connect the cavernous sinus with the pterygoid and pharyngeal plexuses. (*g*) There is sometimes a small vein passing through the foramen of Vesalius connecting the same parts. (*h*) A plexus of veins passing through the carotid canal and connecting the cavernous sinus with the internal jugular vein.

Besides these two main groups of channels, others are present as, for instance, the communication of the angular and supra-orbital veins with the ophthalmic veins at the inner angle of the orbit.

The various forms of extradural abscess are commonly infections by contiguity. The various forms of arachnoiditis, meningitis and venous sinus thromboses occur because of their contiguity to an inflammatory focus in the bone plus the extension of a thrombotic process along the vascular channels indicated.

Brain abscess is particularly prone to be a lymphatic condition. Perivascular lymphatics are especially found in connection with the vessels of the brain. The latter are enclosed in a sheath, which acts as a lymphatic channel, through which lymph is carried into the subarachnoid and subdural spaces and from which it is returned to the general circulation.

According to Bulson,[29] the infection may be borne directly by the blood stream, or travel along the outside of the vessels as they pass through the bone.

Development and Clinical Course: The development of the intracranial complications and the clinical course of the development of the latter have in most of the instances followed a fairly definite order.

Infection of the Skull. The first stage is comprised of the infection of the skull and of the development of the localized or, more commonly, diffuse form of the osteomyelitis with or without abscess formation under the scalp. In some of the cases the bone lesion is localized at the time the intracranial complication appears; in others, the osteitis has become diffuse; in very rare instances little or insignificant changes can be discerned in the bone. Luc was able to find twenty-five cases in which the intracranial lesion appeared while the osteitis was confined to the frontal bone.

Extradural Abscess. The second stage is marked by the occurrence of an external pachymeningitis. This occurs by contiguity and continuity of structure; or the transmission occurs through the vascular channels or through minute openings in the bone. The extradural infection may be at some little distance from the location of the lesion in the bone. Abscess formation is the rule. When small, the symptomatology is lost in the general clinical picture. When the abscess is sufficiently large, signs of intracranial compression become evident. The

latter may be confounded with that derived from other intracranial lesions such as brain abscess.

Should the extradural abscess communicate with the outside of the cranium through a spontaneous or operatively produced opening, and the drainage be sufficient, the physical evidences of the lesion consist in the fungous appearance of the exposed dura mater. In the absence of any drainage, or in the presence of insufficient drainage, the process almost regularly goes on to the next stage.

The third stage is a progression of the second, and according to most of the observers is produced fairly rapidly. A subdural infection occurs, and arachnoiditis and meningitis result.

Arachnoiditis; Meningitis. A serous meningitis is temporary and most commonly only precedes a more alarming condition, or less commonly disappears spontaneously and fairly rapidly. The symptomatology is exactly like that of other well established forms of meningitis; the laboratory findings differ in the important item that no organisms are demonstrable in the spinal fluid.

True arachnoiditis and meningitis in which organisms are demonstrable in the available exudate may develop directly underneath the area of osteitis or at a distance from it; the condition may be localized or may spread with rapidity over the entire brain. Luc says one variety remains localized and does not show any tendency to diffusion, and that in these cases good results may be obtained from an early and efficiently performed operation.

In the further spread of the infection beyond the three stages outlined, the process spreads to the brain and to the large venous sinuses.

Brain Abscess. Brain abscess is a common secondary complication in the fatal cases of this disease reported in the literature. The lesion is essentially similar to brain abscesses of other etiology. The abscess may be so small during the initial stage that it cannot be found on exploratory puncture, while in other cases it may occupy a large part of the lobe and may even extend behind it. The pus may be creamy or serous yellowish, green or brown, as in brain abscess of other etiology; an encapsulating membrane is sometimes present. These abscesses may be independent of any operation, and may result from the progressive extension of the infection and of the resulting lesions to the cerebral parenchyma. In some cases a previous traumatism of the cranium plays a part in the genesis of both the sinusitis and the intracranial infection.

The various stages outlined here do not always occur. In Knapp's [81] case in which the postmortem examination showed brain abscess as well as sinus thrombosis, there was no meningitis. This is rather unusual. A number of cases have been reported in which the brain abscess

81. Knapp, Arnold: Arch. Otol. **32**:181, 1903.

extended either into the arachnoid space or into ventricles. Röpke [25] reported two cases in which the abscess ruptured into the ventricle. These are necessarily fatal accidents. In cases of unilateral frontal sinusitis, if an abscess of the brain forms, it invariably occurs in the frontal lobe of the corresponding side. When such an abscess occurs spontaneously, it develops secondarily to extradural suppuration which is secondary to a perforation or a necrotic osteitis of the deep wall of the sinus.

Fever is the principal symptom of intracranial infection, and there are the usual secondary symptoms of loss of appetite, loss of weight and pallor. The fever is not usually very high.

Later, there are symptoms of intracranial compression. There is headache accompanied by tenderness of the region on pressure or on percussion. The headache may be lacking in exceptional cases, while in others it may be extremely severe. It is usually in the frontal region. The patient may have alimentary or bilious vomiting, and vertigo may occur. One of the most characteristic symptoms is slowness of the pulse. There may be modifications of the pupil, such as papillary stasis or atrophy of the retina. Choked disk—papillitis, neuroretinitis—are common. There are intellectual disorders, consisting of apathy and indifference. Owing to this semi-unconsciousness, many patients have incontinence of urine and feces. Delirium has been reported. It is usually mild, but in some cases there is restlessness, and the patient may attempt to rise from his bed. Unless an operation is performed within a reasonable time, coma appears and is fatal. Tonic and clonic convulsions are rare. There may be an increase in the intracranial pressure with spontaneous opening of the abscess into the ventricle or on the surface of the brain.

In other groups of symptoms, there may be clonic spasms on the side of the body opposite to the lesion in the brain. Aphasia has been noted in only a few cases. However, focal neurologic signs of sufficient clarity to indicate definitely well localized brain areas are relatively uncommon with this group of cases. The abscess may also remain latent, and hence the diagnosis is often extremely difficult. Punctures may give negative results.

Abscess of the brain is very rare in the cases of sphenoidal disease. Kramer [47] had one such case and said that there is only one other such case in the literature. I am indebted to him for an abstract of the notes:

> A 13 year old girl, after a "cold" in the head, developed headache, nausea, vomiting, weakness, pallor and impaired vision. Pyuria and hematuria were present, and the sphenoid focus was found while the cause of the renal complication was being looked for. The patient died. Postmortem examination showed: purulent sphenoiditis, basilar meningitis and a tremendous abscess in the right frontal lobe. The pathway of infection was through a perforation in the roof of the right sphenoid, through the dura and into the right frontal lobe.

Intracranial Venous Sinus Thrombosis. A review of the literature makes it apparent, and only a moment's consideration will drive this home to every one, that the proportionate relationship of thrombosis or thrombophlebitis of the venous sinuses to osteomyelitis of the skull secondary to nasal accessory sinusitis, especially of the frontal and sphenoid sinuses, is exactly like that existing between thrombosis or thrombophlebitis of the lateral sinus and middle ear and mastoid disease. The similarity, therefore, extends in other particulars—pathogenesis, mechanism, clinical course, etc.

Thrombosis of the Superior Longitudinal Sinus. Five cases of thrombosis of the superior longitudinal sinus complicating osteomyelitis of the skull were listed by Killian in 1900. In 1909, Gerber also listed five cases, and in the same year Luc was able to collect fifteen cases. Cases were reported by Frankel,[82] Macewen-Miller,[83] Knapp,[81] Roth[84] and others. In 1914, Eckstein[85] collected fourteen cases of superior longitudinal sinus thrombosis complicating nasal accessory sinus disease, but an osteomyelitis was present in only six of these. Since then every year sees the reports of a few cases, usually about five or six a year. It seems, therefore, that longitudinal sinus thrombosis is not as infrequent as is commonly supposed, and that in any case in which osteomyelitis complicates the nasal accessory sinus disease, thrombosis is to be looked for; unfortunately, from the experience in the literature, the search will result successfully in a large percentage of the cases, especially as knowledge of the frequency of this complication is spread among the medical profession.

Thrombosis of the superior longitudinal sinus occurs most frequently with osteomyelitis of the frontal bone and of the skull associated with frontal and fronto-ethmoidal sinus disease. Sometimes it is found in association with other thromboses.

There are three distinct mechanisms by which this complication occurs primarily:

(1) By contact because of contiguity of structure. The superior longitudinal sinus abuts on, and is closely related to, both frontal sinuses; its anterior narrow portion reaches up to the foramen cecum.

(2) More important, the direct vascular connection between certain segments of the mucosa of the frontal sinuses and of the superior longitudinal sinus.

The venous circulation and the venous inflow into the superior longitudinal sinus is, according to Gray, as follows:

> Into the superior longitudinal sinus the ethmoidal veins originating from the mucosa of the frontal sinuses and from the lateral and medial region of the nasal

82. Frankel, quoted by Luc (footnote 5).
83. Macewen-Miller, quoted by Luc (footnote 5).
84. Roth, quoted by Luc (footnote 5).
85. Eckstein: J. Laryng., Rhin. & Otol. **27**:275, 1914.

mucosa empty. Another vein originating from the antero-lateral portion of the nasal mucosa and accompanying a branch of the anterior ethmoid artery passes through the lamina cribrosa; here it either empties into the venous plexus of the olfactory tract or it empties directly into a large vein of the orbital lobe of the brain which in its turn empties into the superior longitudinal sinus. From the frontal bone the venous blood reaches the superior longitudinal sinus through the frontal diploe which anastomose with the frontal vein. The superior longitudinal sinus receives the venous blood of all superficial veins of the hemisphere; also a few veins of the dura mater empty into it; finally it must be mentioned that in the parietal bone there is present an opening through which the superior longitudinal sinus anastomoses with the veins of the parietal region by way of the parietal emissary veins. As seen from the above, a rather extensive vascular system is connected with the superior longitudinal sinus. The phlebitis from the sinus may extend to all these veins and may give rise to many complex disease pictures.

If the anterior end of the superior longitudinal sinus is injected, numerous fine bony venules together with the mucous membrane lining certain regions of the frontal sinuses are filled with the injected substance.

In the cases of this nature which have been described in the literature, it has been pointed out that the character of such frontal sinusitis is more or less peculiar, being based on a very virulent infection, as a result of which an involvement of the superior longitudinal sinus takes place. This type of sinusitis was designated as "sinusitis exulcerans atque abscendens."

(3) By the spreading of a thrombosis or thrombophlebitis from a communicating venous sinus. There are numerous examples of this.

(4) By contact with a secondary complication, usually a discrete extradural abscess, separated and at a distance from the region of the frontal sinuses.

Thrombophlebitis of the superior longitudinal sinus gives rise to a group of characteristic secondary pathologico-anatomic changes. In most of Luc's [5] cases pus was found at autopsy in the superior longitudinal sinus, and in only one of his five cases the phlebitis extended to the transverse sinus. Intradural changes coexist in practically every case and usually lead to death. They have the character of circumscribed, unilateral or bilateral suppurative meningitides of the convexity of the brain. There may occur a formation of symmetrically situated inflammatory foci in the frontal lobes.

According to Killian [44] and other observers, the symptomatology of thrombophlebitis of the superior longitudinal sinus is quite variable. In most of the cases the disease under consideration does not give rise to severe intracranial symptoms prior to the appearance of the meningitis. In some cases meningitic symptoms are apt to appear several days before death. In some of the reported cases severe symptoms were present for only a few days, because the course of the disease was very short. Although an inflammation of the superior longitudinal sinus

gives rise to severe intracranial symptoms, the complex is not always symptomatic. In most of the cases of this type there may be found tenderness in the region of the parietal bones.

My own experience with this lesion is small. Thrombophlebitis of the superior longitudinal sinus does not appear to have been diagnosed up to the present time in cases of frontal sinusitis. Signs of this special localization are found only with difficulty. From the point of view of a focal neurologic lesion, thrombosis of the superior longitudinal sinus may be suspected when there is a tendency to, or a well established bilateral rigidity of, the extremities, confined to the lower or upper extremities alone, or existing in all four.

Luc [5] believes that the presence of this thrombophlebitis should be considered in cases of pyemia coinciding with an extension of the osteomyelitis to the vertex. I believe this to be a good clinical point as these venous thromboses are associated with general infections, though, curiously enough, positive blood cultures are rather uncommon with isolated thrombosis of the superior longitudinal sinus.

At the present writing, the complication is hopeless from a therapeutic point of view. Unsuccessful attempts have been made to open and drain the sinus.

Cavernous Sinus Thrombosis. Thrombosis of the cavernous sinus is less frequently encountered than thrombosis of the superior longitudinal sinus. The recent literature contains case reports by Faulkner,[86] Fotiade and Antonesco,[87] Guerra,[88] Quincy,[89] Todd,[69] Kramer [47] and others. The impression is given that this variety of intracranial sinus thrombophlebitis is also somewhat more frequent than is generally supposed.

Thrombosis of the cavernous sinus occurs with especial frequency in osteomyelitis of the sphenobasiocciput after sphenoid disease; such bone disease in the base of the skull is almost invariably associated with thrombosis or thrombophlebitis of the cavernous sinus. As a secondary involvement, cavernous sinus thrombosis is frequently mentioned in association with other thromboses of the intracranial venous sinuses, especially of the superior longitudinal sinus.

The mechanism for the production of the primary cavernous sinus thrombosis includes the following:

(1) By contact and contiguity with the diseased bone. The sinus lies in intimate contact with the latter.

(2) By contact with an area of meningitis at the base of the skull.

86. Faulkner, quoted by Luc (footnote 5).
87. Fotiade and Antonesco, quoted by Luc (footnote 5).
88. Guerra, quoted by Luc (footnote 5).
89. Quincy, quoted by Luc (footnote 5).

(3) By vascular extension, especially in cases following tonsilitis or a tonsillectomy. The path lies along the venous plexus in the carotid canal.

The diagnosis of cavernous sinus thrombosis is much more easily made by its dominating symptom of proptosis of the orbital contents. Profound stupor is a characteristic manifestation. Blood cultures are usually negative.

The methods of treatment include:

(1) Ligation of the internal carotid artery.

(2) Eagleton's [48] operation, i. e., evisceration of the orbit and incision and drainage of the sinus.

(3) Kronlein's [90] operation.

Except for one or two spontaneous recoveries and a similar number of recoveries after operation recorded in the literature, this complication has uniformly resulted fatally.

Thrombosis of the other venous sinuses of the skull is much less frequently encountered than thrombosis of either the superior longitudinal or the cavernous sinuses. In the postmortem protocols, the impression is given that the other sinuses are involved secondarily and by extension from the superior longitudinal cavernous sinuses. Abscess formation has been described in the various sinuses.

In the course of the thrombophlebitis of the intracranial venous sinuses, certain stages may be differentiated:

(1) The prodromal stage. In this stage the symptoms are those of the primary lesion, fever, severe pains in the region of the forehead and headaches.

(2) Initial stage. This stage is characterized by pains in the parietal region.

(3) Stage of regional abscess (the disease is not yet generalized). The clinical symptoms of this stage vary, depending on the seat of the extracranial and intracranial abscess. In the presence of an intracranial abscess there are present generalized brain symptoms.

(4) Pyemic stage. This stage is characterized by chills, a remittent fever, pulmonary complications, swelling of the spleen, etc.

(5) The terminal stage. Meningitic symptoms develop at this stage; death occurs after from one to four days.

The terminal stage may follow directly after the initial stage. Stages 3 and 4 may occur simultaneously.

It is important to make an early diagnosis in these cases if the therapy is to be successful. A definite diagnosis can be made during the stage of the regional abscess if the abscess is characterized by

90. Kronlein, quoted by Eagleton (footnote 48).

general cranial symptoms. Pyemic symptoms point definitely to an involvement of the sinus. The condition must be differentiated from meningitis. In cases having a fulminant course, a diagnosis is made only at the autopsy. In the great majority of the recorded cases, and in those few which I have personally seen, many intracranial lesions coexist, and it is impossible at the present time and with the present available knowledge to make any exact differentiations clinically. In every case coming to autopsy one should expect a multiplicity of intracranial complications.

## TREATMENT

The general principles governing the treatment of osteomyelitis in general have been described on a number of previous occasions and will not be repeated here.

In the treatment of osteomyelitis, the importance of prophylaxis is greater for lesions in the skull than for those anywhere else in the body. This is especially so in the extension type of case following nasal accessory sinus disease. Prophylaxis should include these objectives: (*a*) appropriate measures for the possible prevention of any preceding condition to which the osteomyelitis of the skull is commonly secondary; (*b*) the proper immediate care of all scalp wounds, especially those extending into the bone; (*c*) the efficient treatment of all nasal accessory sinus disease, and (*d*) the improvement in the general condition of the patient. When any of these precautions include operative manipulations anywhere near any part of the cranial diploe, extreme care should be exercised not to involve this very vulnerable tissue in the infective process.

### CLASSIFICATION FOR TREATMENT

In osteomyelitis of the skull the cases can be divided into the following groups, as far as the necessary treatment is concerned: (1) cases with the clinical signs of a general infection; (2) cases with little or no signs of a general infection, but with various grades of a local restricted or circumscribed lesion; (3) cases of diffuse spreading osteomyelitis of the skull and (4) cases with intracranial complications.

*Cases with General Infection.*—Highly fulminant forms of general infection (sepsis, septicemia, etc.) are usually of such a high order of severity as to make futile any therapeutic endeavor. They are also commonly associated with a variety and diversity of intracranial complications (meningitis, sinus thrombosis of the longitudinal or cavernous sinuses etc.), each one of which by itself is, practically speaking, beyond one's efforts to cure except for a few fortunate cases reported in the literature.

In less highly fulminant cases it frequently happens that attention to the local bone lesion results in an amelioration of the clinical picture and

a subsidence of any accompanying general infection. The periods of remission which are commonly seen are most frequently related to revisions of the local condition. However, it is only too common also for recrudescences to follow subsequently with an eventful fatality.

*Cases with Local Circumscribed Lesions.*—Cases of this type lend themselves to efficient treatment only when they are in the vault and the neighboring parts of the skull, including the mastoid, and adjacent parts of the occipital bone posterior to the foramen magnum, the accessible parts of the orbital boundaries including the ethmoid, the lacrimal bone, the nasal process of the superior maxilla and the part of the sphenoid that presents in the roof of the nasopharynx.

Efficient treatment of this class of lesion requires the thorough removal of all infected bone, preferably by removal en masse with the line of resection in healthy tissue at an appreciable distance from the infected bone. The dura should not be opened purposely, and the accidental opening of it is a most deplorable accident. The venous sinuses also should not be tampered with unless there is clinical and operative evidence of thrombosis; then, whenever possible a technic similar to that in use for similar conditions in the lateral sinus complicating mastoid disease should be employed.

At any other area away from the vault of the skull efficient complete removal of the disease is commonly impossible; this applies with special force to disease in the ethmoid and in the sphenoid; incomplete operations should be fortified by wide and free drainage, but it must be freely admitted that in these areas the prime indication of complete removal of the disease is never met, and recrudescences are common and frequently of ominous character.

The base of the skull, especially the area comprised in the adjoining parts of the posterior part of the body of the sphenoid, the petrous pyramid and the basiocciput are beyond reach by surgical means; the parts are inaccessible. The danger of uncontrollable hemorrhage is very great; the danger of injury to important nerves is equally large, and the chances of a secondary intracranial infection is almost 100 per cent.

No matter where the disease exists, if it once involves the diploic tissue and veins, a condition is present in which the progression of the lesion seems to be independent of all ordinary therapeutic measures. The lesion is a progressive, self limited one—all too frequently limited by death—in which there is a continuous, contiguous molecular advance of the process, or a diffusion of the infection by repeated series of thrombo-embolisms by which additional areas, separated from the main seat of the disease by slight intervals, are attacked and involved. It is for this reason that it is imperative to remove by operation wherever possible every bit of tissue carrying any infection; the resection should

be very wide, and it is much better to err on the more radical side and remove more, than to remove less and subject the patient to the danger of recurrence. Anything less than complete removal invites disaster. Clinical experience bears this out; the possibility for complete cure is limited to cases in which the diseased area is present only in the accessible regions of the vault of the skull; at the base of the skull in the spheno-petro-basiocciput the mortality is, practically speaking, 100 per cent because removal of the basic infection is not possible.

*Cases of Diffuse Spreading Osteomyelitis of the Skull.*—Diffuse spreading osteomyelitis of the skull is the corollary of the remarks made in the preceding paragraph. Its presence is due to insufficient checking of the lesion by operative means, and its cure depends on the capability and possibility for complete removal of the infected area.

I am under the impression—and I am sorry that I have not up to the present had the opportunity of carrying out the method—that in these cases the maggot treatment of osteomyelitis might be valuable. I mention it here for what it is worth and hope that the method will soon have an opportunity to prove itself in these otherwise difficult cases.

*Cases with Intracranial Complications.*—The treatment of the various complications that have been outlined in this communication depends on the various individual or associated lesions encountered, which are either beyond reach at the present moment—as in some of the venous sinus thrombosis cases—or are reached according to well established principles. It is beyond the scope of this paper to go into the latter at any length, except for the therapeutic indications that accompany the development of a meningitis.

In any case of osteomyelitis of the skull, one should constantly be on guard for the occurrence of meningitis. Continued headache, vomiting and slow pulse should be accepted as prodromal signs of some impending intracranial complication until the assumption is definitely disproved. Rigidity of the neck, a Kernig sign, restlessness and hyperexcitability should intensify one's suspicions. The association of these subjective and objective symptoms should indicate the extreme urgency of the condition. A spinal tap should be done immediately; two possibilities are present:

1. Spinal fluid is obtained in increasing amounts which show on microscopic examination an abnormal number of pus cells, but the absence of any organisms. This is the stage of meningeal irritation and indicates that an inflammatory lesion is in close contiguity with the meningeal membranes.

In the absence of signs pointing to the presence of other intracranial lesions—venous sinus thrombosis, brain abscess, etc.—it should be assumed that the abnormality of the spinal fluid represents an irritation

phenomenon, the source of the irritation being in the infected bone tissue of the skull. If subsidence and disappearance of the irritation phenomena are not prompt, and no signs are present pointing to the presence of other associated intracranial lesions, the indication is present to explore the bone on which operation has not been done or to revise that which has already been operated on, to remove from it all diseased tissue and to drain adequately any associated extradural collections of pus.

2. Spinal fluid is obtained freely under increased pressure, which shows on microscopic examination a preponderating majority of pus cells and the presence of few or many organisms which are viable and are easily culturable. This is the stage of established inflammation of the meninges—frank meningitis. Blood cultivations are frequently positive.

Therapy of any kind is usually ineffective in the cases of established meningitis for the following reasons: (*a*) the practical impossibility of controlling this type of meningitis itself; (*b*) the presence of other intracranial lesions—venous sinus thrombosis especially—which are for practical purposes beyond cure at the present time, and (*c*) the presence of an established and progressive general infection as shown by a demonstrable bacteremia.

## MORTALITY

A considerable number of deaths have followed osteomyelitis of the skull. The fatal issues have resulted from the following circumstances: (1) the intensity of the local lesion, its persistence and the tremendous facility and ready opportunity for the spread of the disease, (2) the readiness with which exacerbations of infection occur in the primary lesion in the extension group of cases, leading to similar exacerbations in, or to the renewed spread of, the osteomyelitis in the cranium; (3) the extraordinary difficulty in adequately removing the disease; (4) the extreme frequency of intracranial complications which furnish the largest proportion of the fatal cases, and (5) the occurrence of general infection (bacteremia, sepsis, septicemia, etc.).

Difficulty in correctly appraising the numbers of patients "cured" and "not cured" and the fatal cases is mostly due to the fact that the condition is marked by many remissions, and the patients naturally drift many times from hospital to hospital and from clinic to clinic. An idea of the correct situation as regards the mortality of osteomyelitis of the skull can be found in the attached statistics:

GERBER.[26]—Total number of cases, twenty-nine; no cures; twenty cases terminated fatally.

MCKENZIE.[27]—Total number of cases, forty-one; twenty-one cases of spontaneous osteomyelitis after nasal accessory sinus disease with fourteen deaths; twenty cases after operation for nasal accessory sinus disease with twenty deaths.

BULSON.[29]—Total number of cases, fifty-five; twenty-seven cases complicating frontal sinus disease with sixteen deaths; eighteen spontaneous cases after frontal sinus disease with ten deaths; nine cases after operation for frontal sinus disease with six deaths.

MOUNT SINAI CASES.—Total number of cases, nineteen; ten cases terminated fatally; in most of the remainder, the patient was discharged for practical purposes "convalescent."

## SUMMARY

The clinical picture presented by the majority of these cases is very similar. The infection arises as a primary or extension process or occurs as a manifestation of a hematogenous infection. It is rare nowadays as a primary disease; it is most common as an extension process after nasal accessory sinus disease; it is relatively rare as a hematogenous infection, and it is least common as a complication of an otologic infection.

The diploe of the bone is invaded by the organisms and osteomyelitis is set up. The infection spreads thence, on the one hand, through the outer table, giving rise to subperiosteal abscesses beneath the scalp; on the other hand, inward, sometimes subsequently giving rise to extradural or subdural abscess, general meningitis, cerebral abscess or to a thrombosis of the longitudinal or other large sinuses.

The dura mater is affected in practically all cases, and the pachymeningitis may remain localized a long time. Thrombosis occurs chiefly in the cavernous, lateral or longitudinal sinuses. The invasion of a large venous sinus is often manifested by emboli with distant metastases. Pneumonia or bronchopneumonia frequently occur.

It is generally easy to make a diagnosis of osteomyelitis in the bones near the orbit or ear. However, it is often difficult to recognize the diffuse form because the general symptoms are often more pronounced and may mask the local symptoms. A diagnosis may be made before operation if a careful study is made of the symptoms that accompany the sinusitis or mastoiditis.

When the osteomyelitis becomes evident, it is necessary to operate, and the operation should be as extensive as possible. The cranial bones should be resected beyond the limits of the lesion. If the wound continues to granulate and if the temperature remains high, sequestrums are present, and they must be removed as completely as possible.

There is a large mortality. The patient succumbs to one or more of these conditions with or without the manifestations of a general blood infection, as evidenced by the presence or absence of a positive blood culture after a varying number of weeks, months or even years.

# POSTOPERATIVE NUTRITIONAL EDEMA

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Nutritional edema has long been recognized as a concomitant of underfeeding and has been accurately described on many occasions in connection with starvation, war edema, beriberi and dysentery. Its close association with insufficient protein intake has received frequent comment, and the similarity between such edema and that seen in so-called nephrosis has been noted by numerous writers. The results of animal experimentation by several investigators have shown clearly a relationship between the production of edema and a lowering of the serum protein, especially in association with very excessive amounts of water and sodium chloride. A fairly complete bibliography on the subject will be found in the review of nutritional edema by Weech and Ling.[1] Very little, if any, attention, however, has been paid to the occurrence of edema following surgical procedures. It is the purpose of this paper to present evidence that nutritional edema is not uncommonly associated with surgical procedures, particularly of the gastro-intestinal tract. We also desire to point out that the very nature of the underlying disease conditions and of the surgical procedures indicated for the their relief lays the foundation for the development of such a complication as an abnormal accumulation of fluid in the tissues.

The data to be presented have been collected from a group of thirty-four patients, twenty-six of whom showed edema of greater or less extent. Most of the patients noted were selected only in so far as they showed clinical edema. They had been treated by generally accepted standard surgical procedures and were given more or less routine postoperative care. The data obtained from the patients will be presented in two groups, those with obvious edema and those with what might be called potential edema. Of the twenty-six patients with edema, twenty-one showed disease of the digestive tract, two had carcinoma of the pancreas and three required surgical interven-

From the Medical and Surgical Services of the Massachusetts General Hospital.

1. Weech, A. A., and Ling, S. M.: Nutritional Edema, J. Clin. Investigation **10**:869, 1931.

tion because of abscess of the lung, cancer of the ovary and sepsis of the joint, respectively. Of the group, two were not operated on but are included because of a potential surgical condition. The cases in this group are presented in table 1. In seventeen instances there was a preceding history of anorexia, undernutrition or intermittent vomiting of several weeks' duration. The five patients operated on for acute appendicitis were previously well. They all had ruptured appendixes. Postoperative drainage was profuse in each instance. Eight patients had observed edema of the extremities before operation. The postoperative edema was noted as a rule about seven days after surgical intervention. It was seen as early as two days after operation and as late as fifteen days after. Once it was noted at operation. Edema was present in every case and varied in degree only. Those showing moderate edema usually manifested it in the ankles, legs or genitalia. In those cases with the most marked edema there was an accumulation of fluid in all the dependent portions of the body, the peritoneal cavity, the walls of the digestive tract and mesentery and the lungs. In nine patients only slight pitting edema of the legs and ankles or of the genitals was noted. The remainder showed edema up to the point of anasarca. Five had definite edema of the lungs, and in two of these oxygen therapy was necessary. Edema of the stomach or intestinal wall was known to have been present in three cases, and because of postoperative vomiting or gastric stasis as indicated by lavage, it was thought that eight patients gastro-enterostomized patients had edema of the stomach, of the gastro-enterostomy stoma or of the intestine, with resulting partial obstruction. Four patients, at least, had diarrhea as a result of edema of the intestinal wall. One patient died directly as a result of the edema of the intestinal wall with resultant partial obstruction. Two other patients were temporarily in a critical condition as a result of the generalized edema and would undoubtedly have died if diuresis had not been obtained.

Blood analyses, usually made at the time edema was noted, included determinations of serum protein, serum albumin, nonprotein nitrogen and chlorides. Unfortunately, all four determinations were not made in every instance, but for the most part the chemical studies were reasonably complete. In nearly every instance there was no evidence either before or after operation of any abnormality of renal function. The exceptions will be specifically mentioned. The only urinary finding of importance was a rather striking elevation of the specific gravity. The surgical procedures included gastro-enterostomy, with or without partial gastric resection, appendectomy with drainage, cholecystoduodenostomy, surgical drainage of sepsis and exploratory laparotomy. Postoperative care included routine surgical measures, including the administration of fluids by various routes. Fluids by mouth were

TABLE 1.—*Data on Patients with Demonstrable Edema Following Surgical Procedures*

| Case | Age | Diagnosis | Operation | Serum Albumin, Gm. | Serum Protein, Gm. | Nonprotein Nitrogen, Mg. | Chlorides, Mg. | Edema |
|---|---|---|---|---|---|---|---|---|
| 1 | 48 | Obstructing ulcer | Posterior gastro-enterostomy | ... | 6.5<br>5.8 | 80<br>47 | 608<br>590 | + |
| 2 | 65 | Obstructing ulcer | Posterior gastro-enterostomy | 3.0 | 5.5 | 20<br>27 | 585 | + |
| 3 | 52 | Cancer of stomach | Exploratory | 3.4 | 5.1 | 41 | 616 | + |
| 4 | 44 | Cancer of stomach | Exploratory | 2.5<br>3.1 | 4.7<br>5.2 | 41<br>26 | 632<br>578 | + |
| 5 | 52 | Cancer of pancreas | Cholecystoduodenostomy | 2.2<br>4.2 | 4.4<br>5.8 | 23<br>32 | 517<br>462<br>509 | +++ |
| 6 | 63 | Cancer of pancreas | Exploratory | ... | 4.5 | 125 | 892 | + |
| 7 | 45 | Gastric ulcer | Posterior gastro-enterostomy | ... | 5.3<br>5.0 | 37<br>32 | 661<br>695<br>622 | + |
| 8 | 55 | Cancer of stomach | Resection | ... | 4.7<br>5.6<br>4.6 | 28<br>23 | (585) | ++ |
| 9* | 47 | Gastric ulcer | Resection | ... | 4.4<br>4.4 | .. | 488<br>574 | ++ |
| 10 | 38 | Cancer of stomach | Resection | 1.9<br>3.6<br>2.4 | 3.7<br>5.6<br>4.4 | 45<br>37<br>40 | 665<br>524<br>609 | +++ |
| 11* | 57 | Cancer of stomach | Resection | ... | 6.2<br>4.4<br>6.5 | 35<br>25<br>27 | 512<br>622<br>570 | ++++ |
| 12 | 62 | Gastric ulcer | Posterior gastro-enterostomy | ... | 4.5 | 50 | 658 | ++++ |
| 13 | 60 | Cancer of stomach | Posterior gastro-enterostomy | ... | 7.0<br>5.5 | 40 | 538<br>606 | + |
| 14 | 60 | Cancer of stomach | Posterior gastro-enterostomy | 3.3 | 7.4<br>5.7<br>7.2 | 43<br>30<br>110 | 506<br>579<br>468 | + |
| 15 | 43 | Perforated appendix | Drainage | 2.9<br>4.8 | 5.2<br>6.8 | 39<br>30 | 555 | ++++ |
| 16 | 13 | Perforated appendix | Drainage | 3.0<br>3.5 | 4.9<br>5.6 | 23<br>22 | 561<br>555 | + |
| 17 | 28 | Perforated appendix | Drainage | ... | 5.5 | 30 | ... | + |
| 18 | 14 | Perforated appendix | Drainage | 3.5 | 4.4 | 41 | ... | ++ |
| 19 | 15 | Perforated appendix | Drainage | ... | ... | .. | 541 | ++ |
| 20 | 60 | Fecal fistula | Closure | 3.9 | 5.5<br>7.0 | 36 | 596 | + |
| 21 | 39 | Lung abscess | Drainage | 1.6<br>3.0 | 5.6<br>6.4 | 32<br>22 | 588<br>570 | ++ |
| 22* | 52 | Cancer of ovary | Resection | ... | 4.7<br>4.1<br>5.6 | .. | (495)<br>557 | ++ |
| 23 | 50 | Cancer of intestine ? | Appendectomy; diarrhea | 2.9<br>2.6 | 5.5<br>3.1 | 55<br>20 | 692<br>608 | +++ |
| 24 | 48 | Cancer of intestine ? | Diarrhea | 1.4<br>2.1 | 4.0<br>3.1 | 41<br>28 | 547<br>515 | +++ |
| 25 | 49 | Joint sepsis | Drainage; transfusion; reaction | 3.3<br>2.6<br>4.2<br>4.0 | 5.5<br>4.4<br>7.3<br>6.5 | 195<br>260<br>91<br>83 | 562<br>628<br>564<br>564 | +++ |
| 26 | 45 | Duodenal ulcer | Hemorrhage | ... | 4.4<br>6.2 | 22 | 508 | +++ |

* The data on these patients who were being cared for at the New England Deaconess Hospital were made available through the courtesy of Dr. Leland S. McKittrick.

usually restricted. Rectal taps were either of water or of physiologic (0.9 per cent) solution of sodium chloride combined with 5 per cent dextrose. Hypodermoclysis consisted in the administration of 2.5 or 5 per cent dextrose in physiologic solution of sodium chloride. Fluids for intravenous administration were, with rare exception, physiologic solutions of sodium chloride containing 5 or 10 per cent dextrose.

It will be seen from table 1 that with few exceptions the degree of edema varied inversely with the serum protein content and somewhat less consistently with the serum albumin. The level of the nonprotein nitrogen bore no relation to the presence of edema, and for the most part the figures obtained were within normal limits, or only slightly above normal. Three notable exceptions occurred in cases 1, 6 and 25. Values for blood chloride interestingly enough were normal or well above normal in over two thirds of the cases, probably because of the administration of large amounts of sodium chloride. The specific gravity of the urine was high in nearly all the cases at or near the time that edema was noted. It ranged from 1.015 to 1.040, with the majority of the figures between 1.025 and 1.035.

With the foregoing facts in mind, it will be of value to consider several of the cases in greater detail. Protocols of some of the more striking cases follow.

## REPORT OF CASES

CASE 12.—A man, aged 62, had a condition diagnosed obstructing pyloric ulcer. For fifteen years he had had intermittent ulcer. Successful intensive medical treatment had been given twenty-one months previous to admission. Generalized edema at this time was relieved while the patient was receiving ulcer therapy. There had been intermittent vomiting for three months, with marked anorexia and some loss of weight.

Physical examination on admission gave essentially negative results, except for edema of the legs, genitals and abdominal wall. Studies of renal, hepatic and cardiac function all were negative. The preoperative serum protein was 5.7 Gm. per hundred cubic centimeters; nonprotein nitrogen, 43 mg., and chlorides, 599 mg.

Edema disappeared with rest in bed and a fair intake of milk and cream.

Posterior gastro-enterostomy was performed for a partially occluding pyloric ulcer. During the first seven days after operation there was obvious gastric stasis, which was relieved by vomiting or gastric lavage. The urinary output was moderate in amount, averaging from 800 to 900 cc. per day, and the specific gravity was high throughout (from 1.030 to 1.034). On the seventh day after operation edema developed rapidly in the feet, thighs and scrotum, and increased in degree after the next week. Digitalization produced no diuresis. The urine was normal, except for the high specific gravity. The vomiting, which had diminished in severity, again became troublesome, and, in addition, on the tenth day a very watery diarrhea developed. Pulmonary edema was evident on the thirteenth day, and the patient died on the following day.

Autopsy showed the local operative findings, anthracosis and anasarca. The walls of the jejunum and ileum were very edematous, and the cause for the malfunctioning gastro-enterostomy was obviously edema of the intestinal wall.

A summary of the fluid intake during the first seven days after operation is important. The patient received the following fluids:

| | | | |
|---|---|---|---|
| Intravenous administration. | 3,900 cc. | Total fluid intake..... | 29,500 cc. |
| Subpectoral ..... | 10,500 cc. | Vomitus ..... | 2,000 cc. |
| Oral ..... | 5,400 cc. | | 7) 27,500 cc. |
| Rectal ..... | 9,700 cc. | | |
| | | Average daily fluid intake. | 3,928 cc. |

The intravenous and subpectoral solutions were made up of dextrose in physiologic solution of sodium chloride (0.9 per cent) and contained a total of 130 Gm. of sodium chloride. The average daily fluid intake was nearly 4 liters and contained at least 18 Gm. of sodium chloride.

On the seventh day after operation the chemical examination of the blood showed: serum protein, 4.5 Gm. per hundred cubic centimeters; nonprotein nitrogen, 50 mg., and chlorides, 658 mg.

CASE 1.—A man, aged 48, had a condition diagnosed obstructing duodenal ulcer. He presented a fairly suggestive history of ulcer for many years. For fifteen months he had had distress in the upper abdominal region relieved by vomiting. The frequency and degree of vomiting increased gradually until admission, with consequent weakness and loss of 30 pounds (13.6 Kg.) in weight. The remainder of the history was irrelevant.

Physical examination revealed an emaciated man. The heart was normal. The abdomen was distended, apparently due to a dilated stomach. There was visible peristalsis. Otherwise the results of the physical examination were essentially negative.

Laboratory examination revealed the following data: urine, normal; red blood cells, 3,090,000 per cubic millimeter; hemoglobin, 60 per cent; serum protein, 6.5 Gm. per hundred cubic centimeters; nonprotein nitrogen, 80 mg.; chlorides, 608 mg.; serum protein, 5.8 Gm.; nonprotein nitrogen, 47 mg., and chlorides, 590 mg.

For four days before operation the patient received a daily intravenous injection of about 1,250 cc. of 10 per cent dextrose in distilled water, and, in addition, an equal amount by oral or rectal administration. Although no sodium chloride was given intravenously, alkaline powders were given for two days before the operation with at least a daily intake of 22 Gm. of sodium bicarbonate. It is to be noted that preoperatively the serum protein had dropped from 6.5 Gm. per hundred cubic centimeters to 5.8 Gm.

On exploration, an obstructing healed duodenal ulcer was found, and a routine posterior gastro-enterostomy was performed. The following operative note was made: "There was much more than the usual amount of fluid in the abdomen. There was very marked edema of the stomach and the transverse mesocolon."

For the first three days after operation the gastro-enterostomy obviously did not function properly, as was evidenced by the amount of vomitus and gastric lavage (1,470 cc.). On the fourth day marked improvement was noticeable, and convalescence was thereafter uneventful. It is of interest to note that no further clyses or intravenous injections were administered after the third day.

A summary of the fluid intake during the first three days after operation was as follows:

| | | | |
|---|---|---|---|
| Intravenous administration.. | 1,750 cc. | Total fluid intake..... | 9,350 cc. |
| Subpectoral ..... | 5,800 cc. | Vomitus ..... | 1,470 cc. |
| Oral ..... | 1,800 cc. | | 3) 7,880 cc. |
| | | Average daily fluid intake. | 2,627 cc. |

The total amount of sodium chloride given by intravenous injection and by hypodermoclysis was 68 Gm., or an average daily amount of 22.6 Gm.

CASE 10.—A woman, aged 38, had a condition diagnosed cancer of the stomach. Her history was essentially unimportant until seven weeks before admission, at which time she began to have vague pain in the upper abdominal region without relation to meals. Vomiting without hematemesis accompanied the abdominal distress and, subsequently, marked constipation. She had lost about 60 pounds (27.2 Kg.) during the eight months before admission.

Physical examination showed an emaciated woman with a palpable mass the size of a hen's egg in the region of the stomach. There was slight pitting edema of the extremities. Roentgenograms of the gastro-intestinal tract showed an obstructive pyloric lesion with complete retention of the motor meal.

Exploration revealed a nodular growth involving the antrum, with regional glandular involvement. A large resection and a posterior gastrojejunostomy were performed. During the six days after operation the patient was able to take only small amounts of fluid by mouth but received by various routes a total of 17,000 cc., or a daily average of 2,840 cc. The daily average salt intake was approximately 19 Gm.

On the fifth day after operation there were signs at the bases of the lungs, and twenty-four hours later cyanosis was extreme enough to necessitate an oxygen tent. The signs were not those of partial collapse or of pneumonia, but were more consistent with pulmonary edema. Three days later there was massive edema of the hands, feet, legs and flanks. Three transfusions of 500, 600 and 600 cc. were performed in the next five days, during which period there was marked abdominal distention and watery diarrhea. At this point severe stomatitis developed, similar to that noted in case 15. Following the third transfusion the edema diminished slightly, but there was evidence of increasing pulmonary edema and gastric retention, as demonstrated by gastric lavage yielding 780 cc. The patient died on the fifteenth day after operation.

Autopsy showed in addition to the operative findings and a walled-off abscess between the stomach, liver, colon and anterior abdominal wall, evidences of edema of the legs, vulva, pleural cavity and lungs. There was about 1,000 cc. of thin yellow fluid in the peritoneal cavity, which may have been associated with nutritional edema or with the inflammatory process in the abdominal cavity or with both. Microscopic examination of the lungs showed many of the alveoli filled with serum and slight edema of the submucosa in the intestine.

Chemical examination of the blood revealed the following: Eight days after operation, the serum protein was 3.7 Gm. per hundred cubic centimeters; serum albumin, 1.9 Gm.; nonprotein nitrogen, 45 mg., and chlorides, 665 mg. A transfusion of 500 cc. of blood was given.

Ten days after operation the serum protein was 4.2 Gm. per hundred cubic centimeters; nonprotein nitrogen, 36 mg., and chlorides, 621 mg. A transfusion of 600 cc. of blood was given.

Twelve days after operation the serum protein was 4.4 Gm. per hundred cubic centimeters; nonprotein nitrogen, 37 mg., and chlorides, 602 mg.

A summary of the fluid intake during the first six days after operation is as follows:

(Hypodermoclysis, 1,000 cc. one day before operation)

| | | | |
|---|---|---|---|
| Intravenous administration. | 3,900 cc. | Total fluid intake..... | 17,080 cc. |
| Subpectoral ..... | 10,500 cc. | Daily average ..... | 2,846 cc. |
| Oral ..... | 5,400 cc. | | |
| Rectal ..... | 2,880 cc. | | |

The average daily intake of sodium chloride was 22.9 Gm.

CASE 11.—The patient, aged 57, had a condition diagnosed cancer of the stomach. The past history was irrelevant. For two months the patient had suf-

fered from epigastric distress, nausea, and finally obstructive vomiting. Physical examination revealed an emaciated patient with an obviously enlarged stomach and a palpable mass in the region of the pylorus. Roentgenograms showed a grossly obstructive lesion at the lower end of the stomach. Operation was decided on, and at exploration a large obstructing lesion was found; a very wide resection was performed together with an anastomosis between the jejunum and the remainder of the stomach. The wall of the stomach was very edematous.

On the day preceding the operation the patient received an intravenous injection of 750 cc. of dextrose in physiologic solution of sodium chloride, and on the day of operation 4,000 cc. by clysis and by vein. The serum protein on this day was 6.2 Gm. per hundred cubic centimeters. Four days later the serum protein had dropped to 5.2 Gm., and the blood chlorides had risen to 611 mg. Three days later, or six days after the operation, the serum had reached a level of 4.4 Gm., and the blood chlorides were at the level of 578 mg. During this seven day period the average daily fluid intake was 3,187 cc., 2,070 cc. of which was introduced by vein or by clysis, with a salt intake of 18.6 Gm. a day. Edema of the feet and left arm was noted on the second day after operation, and by the fifth day anasarca was present, involving even the cheeks and lips. From the third day after operation the fluid intake was reduced steadily, until on the seventh day after operation it amounted to only 860 cc. With the marked reduction in the administration of fluid and salt, diuresis was prompt, and the demonstrable edema, which had reached its peak coincidentally with the greatest drop in serum protein, receded rapidly. It had completely disappeared by the tenth day, at which time the serum protein was normal. From the third day, however, vomiting was a constant feature, and this may have been due to edema of the stomach and gastro-enterostomy. The vomiting undoubtedly was a contributory factor in the lowering of the blood chlorides to 479 mg. per hundred cubic centimeters.

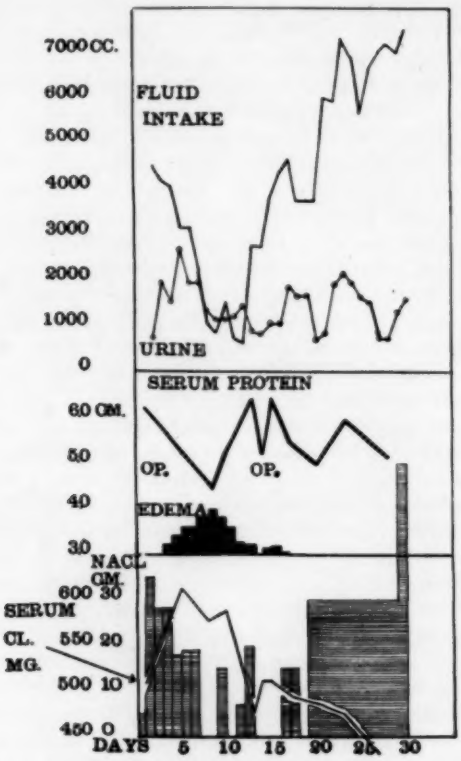
Because of the persistent vomiting, a jejunostomy was resorted to, and for three days moderate edema again returned. As soon as possible after the second operation a generous amount of protein and salt was given by jejunostomy, and this plus transfusion resulted in a temporary rise in serum protein and blood chlorides. Edema did not recur, but complications around the enterostomy resulted in final complete obstruction and eventual death. During the latter period the serum protein and blood chlorides dropped despite an adequate protein and salt intake via the jejunostomy.

A graphic representation of the findings in this case is given in the chart. The time relations between the high fluid and salt intake, the lowering of the serum protein and the development of edema are readily noted.

Case 15.—A woman, aged 43, had a condition diagnosed perforated appendix. The history was essentially unimportant until three days before admission. At this time there was sudden onset of pain in the right lower quadrant with nausea, vomiting, fever and chill. The patient was brought to the hospital where a diagnosis of acute appendicitis was made. Operation was immediately performed. A gangrenous appendix was found; it was removed, and drainage was instituted.

Drainage was profuse for several days. During the first six days after the operation the patient received clyses and intravenous injections of 2.5 per cent dextrose in physiologic solution of sodium chloride aggregating 12,700 cc., or an average daily amount of 2,116 cc. The sodium chloride intake by these injections amounted to 19 Gm. daily. At the end of the sixth day edema of the extremities was noted, and, in spite of discontinuing intravenous injections and hypodermoclysis, it increased rapidly so that on the following day there was anasarca. Cyanosis was so marked from pulmonary edema that an oxygen tent was necessary. Digitalis was given, a common procedure, but presumably was of no value. As

emergency measures, 50 per cent dextrose was given intravenously and 2 cc. of salyrgan. Diuresis was prompt, and in two days there was marked improvement. Five days after the appearance of massive edema the patient received a transfusion of 250 cc. of blood and three days later a second one of a similar amount. Following the two transfusions, diuresis continued for almost a week. From that point convalescence was uneventful. It is of interest to note that severe stomatitis occurred two weeks after operation.




Effect of administration of fluid and salt in the production of postoperative nutritional edema. Observations were made on a patient with cancer of the stomach (case 11). Edema was observed two days following a resection and a gastro-enterostomy, and reached its peak on the ninth day.

A summary of the fluids given for six days after operation and of the laboratory findings is as follows:

| | | | |
|---|---|---|---|
| Intravenous administration.. | 6,200 cc. | Total fluid intake..... | 12,700 cc. |
| Clysis ..... | 6,500 cc. | Average daily fluid intake.. | 2,116 cc. |
| Oral .....Small amount | | | |

The total amount of sodium chloride given by clysis and intravenous injection was 114 Gm., or an average daily intake of 19 Gm.

Six days after operation the serum protein was 5.3 Gm. per hundred cubic centimeters; serum albumin, 3.4 Gm., and nonprotein nitrogen, 39 mg.

Salyrgan, 2 cc., and 50 per cent dextrose were administered intravenously.

Nine days after operation the serum protein was 5.3 Gm. per hundred cubic centimeters; serum albumin, 2.9 Gm., and nonprotein nitrogen, 27 mg.

Two blood transfusions were given of 250 cc. each.

Eighteen days after operation the serum protein was 6.9 Gm. per hundred cubic centimeters; serum albumin, 4.8 Gm., and nonprotein nitrogen, 30 mg.

CASE 17.—A man, aged 28, had a condition diagnosed perforated appendix. The history was unimportant except for a single attack of sharp pain in the right lower quadrant three years previous to admission. Eight days prior to admission the patient had intermittent epigastric pain, associated with nausea and vomiting. Later the pain shifted to the right lower quadrant, and there was further vomiting. He entered the hospital because of the continuation of his symptoms, and a diagnosis of acute appendicitis was made. Operation was performed at once, and an appendical abscess was found which was drained. During the following six days drainage was profuse. During this period the patient received an average of 3,870 cc. daily by intravenous, subpectoral and oral routes. The average daily sodium chloride intake was about 23 Gm. On the third day in particular the fluid intake, by error, was 7,800 cc., with a salt content of almost 62 Gm. The patient showed probable pulmonary edema at the end of the second day, vomited off and on for the next six days, and had pitting edema of the feet at the end of the eighth day. The serum protein at this time was 5.5 Gm. per hundred cubic centimeters and probably had been lower a few days previous. At this point he was able to take a reasonable amount of protein by mouth and convalescence was thereafter uneventful.

A summary of the fluid intake for six days after operation is as follows:

| | | | |
|---|---|---|---|
| Intravenous administration.. | 9,865 cc. | Total fluid intake..... | 24,060 cc. |
| Subpectoral ..... | 5,200 cc. | Vomitus ..... | 1,840 cc. |
| Oral ..... | 8,995 cc. | | 6) 23,220 cc. |
| | | Average daily fluid intake. | 3,870 cc. |

The average daily intake of sodium chloride was 22.6 Gm.

CASE 26.—A woman, aged 45, had a condition diagnosed bleeding duodenal ulcer. Although no operation was performed on this patient, the case is presented because an operation might well have been considered. Her past history was irrelevant. The present illness was of one month's duration and consisted only of indefinite epigastric distress until three days before admission, at which time she passed two large tarry stools and one containing red blood. The following day she vomited a pint of blood, liquid, and passed another tarry stool. The day of admission she vomited three times, each time about a pint and a half of black and reddish vomitus.

Physical examination showed an obese pale woman in no distress. The pulse was 104 and the blood pressure was 150 systolic and 82 diastolic. There was slight edema of the left lower leg.

On admission, her red blood count was 1,550,000 per cubic millimeter with a hemoglobin of 45 per cent. She vomited more blood the following day, and on the seventh day of her acute illness her count had dropped to 1,030,000 and the hemoglobin to 30 per cent. She was given a blood transfusion, but a further hemorrhage occurred, and on the seventeenth day her red count was 950,000 per cubic millimeter with a hemoglobin of from 25 to 30 per cent. On the next day she was given another transfusion and had a severe reaction, characterized by a rise in temperature and a chill. The following day there were signs of pulmonary edema at the base of the right lung, and the next day there was edema of the face, eyelids, hands, legs and trunk. There were signs of pleural effusion on the right side.

During the three weeks preceding the development of edema, the patient had received relatively little fluid by mouth. For a week preceding the development of edema, sodium bicarbonate had been administered in combination with bismuth or calcium carbonate. The amount of alkali administered in combination had been sufficient on the twentieth day to produce a moderate but real alkalosis. Sodium had also been administered in the form of sodium chloride in rectal taps. The total amount cannot be determined.

Chemical examination of the blood revealed the following:

Twenty days after the onset of the illness the serum protein was 4.4 Gm. per hundred cubic centimeters; nonprotein nitrogen, 19 mg.; chlorides, 508 mg., and the carbon dioxide-combining power, 78.8 per cent by volume.

Twenty-seven days after the onset the serum protein was 5.4 Gm. per hundred cubic centimeters and the carbon dioxide-combining power, 59.2 per cent by volume.

Thirty-four days after the onset the serum protein was 6.2 Gm. per hundred cubic centimeters.

From the twentieth day after the onset of her illness, possibly because of a high protein diet given in frequent small feedings, there was gradual diminution in the edema and a good diuresis. There was no further bleeding, and with the subsidence of edema the patient lost 10 pounds (4.5 Kg.) in weight in spite of a gradually increasing food intake. Alkali was discontinued as soon as it was realized that a mild alkalosis existed. In one week after the height of the edema the serum protein was 5.4 Gm. per hundred cubic centimeters, and the carbon dioxide-combining power was 59.2 per cent by volume. One week later the serum protein had risen to 6.2 Gm. Shortly thereafter the patient was discharged, free from edema, and with a red count returning steadily to normal. Roentgenograms of the gastro-intestinal tract showed a duodenal ulcer. The relation of this case to abdominal surgery will be considered later.

Case 25.—The patient, aged 49, had a condition diagnosed sepsis of the joint. Drainage and transfusion had been employed. The history was essentially unimportant except for the present illness. For four years, following a previous operation on the hip, the right hip joint had had continuous drainage of purulent material with resulting local pain and disability. Physical examination showed little beyond the local condition except some general loss of weight. There was no evidence of tuberculosis. Routine laboratory studies were negative.

On September 17, a posterior drainage of the right hip joint was performed. On October 10, an arthrodesis of the hip was done followed by continuous drainage. Two weeks later, because of an anemia of 2,220,000, and in order to hasten convalescence, a transfusion of 600 cc. of whole blood was given. The patient had an immediate and severe reaction followed by fever, chills and vomiting. The next day the vomiting persisted, and the patient was slightly jaundiced. The urine, which was scant and very concentrated, retained a trace of albumin and numerous red cells. For the next ten days the patient had marked oliguria, anorexia and nausea. On November 4, he was vomiting and was extremely dehydrated and somewhat irrational. The urine still continued to show a trace of albumin, and the nonprotein nitrogen was 200 mg. per hundred cubic centimeters. There was edema of the affected leg, which was at first thought to be due to pressure of the cast. Blood studies the following day showed a serum protein of 5.5 Gm. per hundred cubic centimeters, a nonprotein nitrogen of 195 mg., and blood chlorides of 562 mg. It was felt that the condition was essentially one of extreme dehydration following a reaction to the transfusion with a partial renal shut-down, and fluids were given rather freely in spite of the danger of producing edema. Diuresis was promoted by the use of a 50 per cent solution of dextrose in distilled water and by the use of salyrgan. For the next eight days the average daily fluid intake

was 2,800 cubic centimeters, with a total of 36 Gm. of sodium chloride given in two intravenous injections. Edema of the face and leg was obvious on the first day of intensive therapy and rapidly increased, until on the fourth day generalized edema with ascites and pulmonary edema was present. The latter was associated with cyanosis and orthopnea. During the period of eight days the serum protein dropped to 4.3 Gm. and then, as diuresis became established, rose to 6 Gm. The nonprotein nitrogen rose to 211 mg. and did not fall appreciably until ten days after intensive treatment started. The patient vomited persistently and was very irrational for about ten days, and during the first three days was bothered by a severe watery diarrhea. After about the seventh day diuresis was striking, and from then on the edema rapidly subsided. The general condition improved gradually, however, and the nitrogen retention persisted for three weeks after active treatment started. With a return of the blood to normal the urine cleared completely, and convalescence was thereafter uneventful. A tabulation of the important findings follows:

| | Intravenous Administration, Cc. | Total Fluid, Cc. | Serum Protein, Gm. | Serum Albumin | Nonprotein Nitrogen | Edema |
|---|---|---|---|---|---|---|
| November 5..... | 2,100 | 3,300 | 5.5 | 3.2 | 195 | + |
| November 6..... | 1,200 | 2,500 | 4.3 | 2.6 | 260 | ++ |
| November 7..... | 1,900 | 2,900 | 5.5 | 2.6 | 205 | +++ |
| November 8..... | 250* | 2,200 | ... | ... | ... | ++++ |
| November 12..... | Diuresis excellent from November 9 | | 6.0 | 3.4 | 205 | + |
| November 16..... | Liberal fluid intake by mouth | | 7.3 | 4.2 | 91 | ? |
| November 23..... | ..... | | 6.5 | 4.0 | 33 | 0 |

* 25 per cent dextrose.
Salyrgan was given on November 5 and November 6.

In table 2 are given brief data on eight other cases. The patients observed in this group presented conditions similar to those presented in the previous one. In every case but one (no. 32) there was an underlying condition which laid the foundation for marked undernutrition. Case 32 corresponded to the cases of acute gangrenous appendicitis outlined in the preceding group. In each instance there was a marked lowering of serum protein to the critical level. Demonstrable edema was not observed, however, either because the figures for serum albumin did not drop to the critical level, or because fluids and salt were not pushed to sufficiently high levels to produce a noticeable accumulation of fluids. It is obvious, however, that these were all borderline cases in which slight excesses in the administration of fluid and salt would have produced real difficulties.

## COMMENT

A consideration of the foregoing data indicates that nutritional or inanition edema may readily occur as a complication of many surgical conditions. The majority of the patients observed were undernourished prior to operation because of malignancy, pyloric obstruction and similar conditions. Actual vomiting as well as loss of appetite contributed to such a situation. In one instance (case 12) edema had

been noted prior to operation. Following a surgical procedure in every instance the process of undernutrition was continued for several days by the very nature of the operation performed. In addition, the situation was further aggravated by the administration of relatively large amounts of fluids and salt. Table 3 indicates the amounts of fluid administered during the first few days after operation. It will be noted that the actual amount of fluid given daily in the cases of gastric dis-

TABLE 2.—*Data on Patients with No Demonstrable Edema, but with a Lowered Serum Protein, Following Surgical Procedures*

| Case | Age | Diagnosis | Operation | Serum Albumin, Gm. | Serum Nonprotein Protein, Gm. | Nitrogen, Mg. | Chlorides, Mg. |
|---|---|---|---|---|---|---|---|
| 27 | 50 | Obstructing ulcer | Posterior gastro-enterostomy | 3.5 | 7.0 | 92 | 441 |
| | | | | 4.5 | 5.6 | 173 | 569 |
| 28 | 42 | Duodenal ulcer | Posterior gastro-enterostomy | ... | 7.3 | .. | 585 |
| | | | | 3.4 | 5.5 | 25 | 585 |
| | | | | 4.1 | 6.6 | 37 | 555 |
| | | | | 3.8 | 6.1 | 25 | ... |
| 29 | 45 | Gastric ulcer | Resection | 5.5 | 6.8 | 40 | 585 |
| | | | | 4.2 | 5.3 | 26 | 625 |
| 30 | 63 | Ulcerative colitis | Ileostomy | 3.4 | 5.7 | 41 | 603 |
| | | | | 4.1 | 6.3 | 32 | 590 |
| 31 | 57 | Cancer of stomach | Resection | 3.5 | 5.9 | 32 | 699 |
| | | | | 3.4 | 6.5 | 28 | 664 |
| | | | | 3.3 | 5.5 | 25 | 605 |
| 32 | 32 | Acute appendicitis | Drainage | 4.1 | 5.5 | 44 | 602 |
| 33 | 57 | Cancer of stomach | Resection; anterior gastro-enterostomy | ... | 5.5 | 26 | 676 |
| | | | | 3.9 | 4.9 | 36 | 708 |
| 34 | 57 | Cancer of colon | Resection | 3.4 | 5.2 | 39 | 527 |
| | | | | 2.5 | 5.1 | .. | 558 |
| | | | | 3.1 | 4.8 | .. | 646 |
| | | | | 3.1 | 4.3 | 46 | 583 |

TABLE 3.—*Summary of Fluid and Salt Administration in Cases of Gastric and Intestinal Surgery*

| | |
|---|---|
| **Cases of Gastric Diseases, 14; Cases with Edema, 11** | |
| Average daily fluid intake (total) for 5 days | 3,153 cc. |
| Average daily fluid containing sodium chloride (0.9% NaCl) | 1,718 cc. |
| Average daily sodium chloride intake | 15.5 Gm. |
| Average serum protein at time edema noted (range, 3.7-5.8) | 5.2 Gm. per 100 cc. |
| **Cases of Acute Appendicitis with Drainage, 6; Cases with Edema, 5** | |
| Average daily fluid intake (total) for 5 days | 2,619 cc. |
| Average daily fluid containing sodium chloride (0.9% NaCl) | 2,170 cc. |
| Average daily sodium chloride intake | 19.5 Gm. |
| Average serum protein at time edema noted (range, 5.2-5.5) | 5.4 Gm. per 100 cc. |

eases exceeded 3,000 cc. This included the fluid intake by all routes, but by intravenous or subpectoral routes 1,700 cc. was given daily, with a salt content of over 15 Gm. The average daily intake of sodium chloride for a normal person does not exceed from 5 to 6 Gm. a day. A glance at table 1 will suffice to indicate that in only an exceptional case were the blood chlorides below a normal level, and in many instances the figures were abnormally high as a direct result of the administration of sodium chloride. That the amount of sodium chloride given was in excess is also indicated by the abnormally high

urinary specific gravities which ranged between 1.015 and 1.040, with an average about 1.030, in spite of a very adequate fluid output. In some instances there was an associated oliguria, but in many instances there was a good urinary output even in the presence of edema.

In the group of patients with gastroduodenal disease there would seem little reasonable doubt that the situation immediately preceding surgical intervention plus the necessary limitation of all food and an excessive administration of salt and water were the factors involved in the production of edema. The average amount of serum protein noted at the time of the development of edema was 5.2 Gm. per hundred cubic centimeters, which is well below the critical level for the development of edema. The range was between 3.7 and 5.8 Gm. in these cases during the period of edema. The lowering of the serum protein was due first to malnutrition, and second to subsequent dilution of the plasma by excessive amounts of fluid. It would seem that the retention of water in the tissues was dependent on the altered osmotic relations as a result of the foregoing factor, plus the addition of excessive amounts of sodium chloride, resulting in a movement of sodium to the tissues along with water. Such an hypothesis is in accord with the results obtained in numerous experimental observations.[2]

The accompanying chart, presenting findings in case 11, shows graphically what has just been discussed. The protocol of the case indicates that the factors of preceding malnutrition, postoperative starvation and the excessive administration of fluid and salt were all present. Prior to operation the serum protein was apparently at a normal level (6.2 Gm. per hundred cubic centimeters). Such an apparently normal figure is not uncommon in association with dehydration, and may give a false sense of security. Once a slight excess of fluid has been given, the serum protein drops rapidly, as actually happened in this instance. Postoperatively, 21,300 cc. of fluid was given in the first six days, with a total salt content of 147 Gm. Under this regimen the serum protein dropped in four days to a level of 5.2 Gm. per hundred cubic centimeters, and in spite of a marked change in therapy it reached a low level of 4.4. Gm. in four more days. The effect of the administration of such large amounts of salt is reflected in a rise in blood chlorides from a level of 505 mg. per hundred cubic centimeters to one of 610 mg. in four days. Edema of the extremities was noted two days after operation and continued to increase until anasarca was present. This coincided with the lowest figure for serum protein, and in the

2. (*a*) Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930. (*b*) Falta, W., and Quittner, M.: Ueber den Chemismus verschiedener Oedemformen, Wien. klin. Wchnschr. **30**:1189, 1917. (*c*) Footnote 1.

face of a beginning diuresis brought about by a sharp restriction of fluids. As soon as diuresis was established, the edema disappeared rapidly and the serum protein rose. At the time of the second operation jejunostomy was performed, and an adequate protein and salt intake was possible. Vomiting recurred, however, in a few days, and attempts to maintain an equilibrium were not possible. The final drop in chlorides and serum protein was the result of excessive vomiting and diarrhea with resultant loss of fluid, protein and salts.

In the patients (cases 15 to 19 and 32) who developed either visible or "potential" edema following an operation for appendicitis, the factors involved are not quite so clear. There was obviously no question of undernutrition before operation. All the patients had essentially irrelevant histories before the attack of appendicitis and were well nourished. Following operation the excessive administration of fluids and sodium chlorides was as striking as in the first group of cases. The average daily fluid intake for the first five days after operation was approximately 2,600 cc., of which 2,100 cc. was given intravenously or by clysis, with a total sodium chloride content of almost 20 Gm. a day. It is quite possible that an intake of over 2.5 liters of fluid was advisable in view of the elevation of temperature with consequent loss of water but there is little reason to warrant the administration of over 19 Gm. of salt a day for nearly a week. It will be noted that the serum protein dropped to a critical level or below in all of the cases observed. In case 19 no determinations were made, but as it differed in no way from the other five cases it is reasonable to assume that here also there was a similar reduction in serum protein. It is possible that the lowering of the serum protein was due solely to dilution by excessive fluid, especially by the intravenous route. Experimental work by Beard and Blalock [3] would indicate that this may be a partial explanation of this phenomena. The edema noted in these patients was not due to local inflammatory changes in the tissue, and changes in the serum protein obviously were not due to such a cause. There are two other possible factors which may have contributed to the lowering of the serum protein and the development of edema. In each instance, because of the localized peritonitis associated with a gangrenous appendix, drainage was necessarily established and was profuse. Here then was a cause for the lowering of serum protein, namely, loss of serum protein by actual drainage. Whether a coincidence or not, my associates and I have not observed edema in

3. Beard, J. W., and Blalock, A.: Intravenous Injections: A Study of the Composition of the Blood During Continuous Trauma to the Intestines When No Fluid is Injected and When Fluid is Injected Continuously, J. Clin. Investigation **11**:249, 1932; The Effects on the Composition of the Blood of the Subcutaneous Injection of Normal Salt Solution into Normal Dogs and into Dogs Subjected to Intestinal Trauma, Graded Hemorrhages and Histamine Injection, ibid. **11**:311, 1932.

cases of simple appendicitis not needing prolonged drainage. Our own animal experiments now under way would seem to indicate that drainage alone, even in the absence of sepsis, will apparently act as a factor in lowering the protein content of the blood and in the development of edema. In addition, it is conceivable that sepsis, even if localized and properly drained, may cause a greater generalized capillary permeability with the escape of fluid into the tissues. In this group of cases, then, excessive fluid and salt intake, plus loss of protein by drainage, and the possible influence of sepsis on capillary permeability must be considered as the causes of the occurrence of tissue edema. In cases 21 and 25 the loss of protein by drainage probably constituted a real factor in the development of edema. The former case was that of a patient with a draining abscess of the lung, and the latter that of a patient with a draining septic hip.

It is of interest to comment on certain other aspects of the problem as illustrated in some of the foregoing cases. In case 25 undernutrition from chronic sepsis of the joint in association with a marked anemia formed the background of the clinical picture. Following operation on the hip, anorexia became more marked and the anemia increased. A transfusion was indicated and was performed, but was followed by a severe reaction with polyuria, hematuria, jaundice and a subsequent uremic picture. Edema undoubtedly developed because of an underlying severe inanition, coupled with inability of the kidneys to excrete water and salt properly. The serum protein was already at a critical level of 5.5 Gm. per hundred cubic centimeters. In view of the very high amount of nonprotein nitrogen (195 mg. per hundred cubic centimeters) and extreme dehydration, fluids had to be pushed and the edema increased, as was to be expected, coincident with a reduction in the serum protein to 4.4 Gm. per hundred cubic centimeters. Before a diuresis was finally established, anasarca had developed with so much pulmonary edema that the outcome was extremely problematic. Persistent vomiting made it impossible to supply sufficient protein in the diet to raise the serum protein, and further transfusions for the sole purpose of raising the serum protein were refused. Fortunately a diuresis was finally established by the use of salyrgan, and subsequently the edema disappeared with a complete return to normal of the blood values and a complete restoration of kidney function. In this case the mechanism of edema formation was complicated by temporarily disturbed renal function, although the background was essentially that of inanition. As previously noted, drainage from the septic hip may have been an additional factor.

In case 26 the mechanism for the production of edema differed from the preceding cases and is of some interest. As indicated in the case report, no element of undernutrition was present. Three factors seemed to combine toward the lowering of the serum protein and the

accumulation of fluid in the tissues. In the first place there was a tremendous loss of protein associated with a hemorrhage from a duodenal ulcer severe enough to cause the red count to drop to about 1,000,000 cells per cubic millimeter in a few days. This represented an actual loss, only to be replaced by a proper protein intake or by transfusion. The former was impossible because of continued bleeding. The latter was tried, but unfortunately was followed by a fairly severe reaction with some resultant disturbance of kidney function. In addition, during the period preceding the development of edema, the patient received alkalis in the form of powders made up of sodium bicarbonate and calcium carbonate or magnesium oxide. Because of the temporary impairment of renal function, alkali was retained to such an extent that an actual alkalosis developed. In this case the serum protein was lowered primarily by loss through hemorrhage. Alkalosis and renal dysfunction provided the other factors necessary for an accumulation of fluid in the tissues. Diuresis was finally produced by the omission of alkalis and by an increase in the intake of protein by mouth. This case is of additional interest because of the possibility of surgical intervention. Although surgical intervention immediately after a large hemorrhage from a duodenal ulcer is not usually indicated, continued bleeding occasionally necessitates an operation. Under such circumstances the administration of fluids and salt that is normally consequent on gastro-intestinal surgical procedures might conceivably have resulted in edema of even more serious import.

That the finding of a normal amount of serum protein before operation does not constitute a guarantee against the development of edema was noted in several cases, and is best exemplified in case 14. This patient had a typical story of pyloric obstruction from carcinoma, was underweight and dehydrated. An operation, posterior gastro-enterostomy was decided on, and blood studies were made with a view to determining the optimum administration of fluids and salt. The serum protein was 7.2 Gm. per hundred cubic centimeters, nonprotein nitrogen 43 mg. and blood chlorides, 506 mg. In view of the normal serum protein, the slightly elevated nonprotein nitrogen and the low chlorides, it was decided to administer a reasonable quantity of physiologic solution of sodium chloride intravenously during the first few days after operation. For the first eight days an average amount of 1,070 cc. of fluid was given intravenously, with an average daily salt intake of 8.5 Gm. In spite of the rather moderate amounts used, edema developed in eight days and was accompanied by a lowering of the serum protein to 5.5 Gm. per hundred cubic centimeters. Intravenous injections were at once omitted, and the edema disappeared immediately with an associated rise in serum protein to the original level of 7.3 Gm. per hundred cubic centimeters. The carcinomatous process was so widespread that the gastro-enterostomy did not func-

tion satisfactorily, with the result that vomiting persisted, dehydration rapidly returned and death ensued shortly thereafter. As long as intravenous administration of fluids was withheld, the serum protein did not drop again and edema did not develop, regardless of the rapidly advancing starvation. In other words, the normal level of serum protein gave a false idea of the protein content of the tissues and blood, and was lowered rapidly with the administration of fluids. Our own recent experiments have repeatedly borne out the fact that long continued undernutrition, especially with protein deficiency, may be associated with a normal or high figure for serum protein without the development of edema, unless sufficient amounts of fluids and salt are simultaneously administered. Peters [4] has noted such a possibility.

From the foregoing discussion it is evident, we think, that the important factors concerned in the development of nutritional edema after surgical operation are first an underlying condition of undernutrition, although this is not essential, as shown in the cases of appendicitis. In addition, there must be an actual lowering of the serum protein to a critical level by the administration of a somewhat excessive amount of fluid. The administration of sodium chloride or alkaline salts tends to increase the retention of fluids by the tissues. The serum protein may also be lowered by actual loss of blood from hemorrhage. Profuse drainage may accomplish a similar result. Retention of fluid and salt may be further aggravated by temporary renal dysfunction following some such phenomenon as a severe reaction to transfusion. Obviously the food intake after an abdominal operation is limited, and particularly in protein, thus constituting an added factor in the continued maintenance of a low level of serum protein.

In addition to the foregoing considerations, it is important to comment on certain other aspects of the question.

It is obvious from the preceding discussion that in spite of an apparently normal level of serum protein edema may be produced rapidly by the administration of amounts of salt-containing fluid that would ordinarily cause no trouble. The underlying factors of extreme malnutrition and dehydration must, however, be a fundamental background for such an occurrence. It remains to ask what is the actual critical level for serum protein at which edema begins to develop. Van Slyke [2a] and others have apparently shown that a level of 5.5 ± 0.3 Gm. per hundred cubic centimeters constitutes the point where fluid begins to leave the blood and accumulates in the tissues. Serum albumin likewise must fall below a level of 2.5 ± 0.2 Gm. per 100 cubic centimeters before edema develops. Examination of our figures

4. Peters, J. P.; Bruckman, F. S.; Eisenman, H. J.; Hald, P. M., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: VII. A Note on the Proteins in Acute Nephritis, J. Clin. Investigation **11**:97, 1932.

indicates that these figures apply for the most part. Although the actual figures were undoubtedly not obtained at the moment edema began to occur, in most instances the time relation between the two was fairly close. In nearly every instance the serum protein was at or below the so-called critical level when edema was noted. An interesting fact may be noted in case 23. In this patient the serum protein was on numerous occasions below 3.5 Gm. without any associated edema. In this case an intractable diarrhea prevented sufficient absorption of water to occur to permit the development of edema even in the presence of an extremely low amount of serum protein, again emphasizing the importance of other factors than malnutrition alone. This was also the case in the terminal stages of case 11 in which the serum protein dropped to 4.4 Gm. per hundred cubic centimeters without the recurrence of edema.

From our observations one cannot determine whether the intravenous administration of fluid and salt causes a greater tendency to edema than rectal administration. It probably is true that either of these routes will aid in the development of edema more quickly than the oral or rectal administration. It is also true that postoperatively the two former methods are of necessity the methods of choice for the maintenance of an adequate prolonged fluid intake. Some experimental work [3] would indicate that intravenous administration of fluid causes a more rapid drop in serum protein and a correspondingly more rapid passing of fluid into the tissues.

It is of some interest that in at least two instances the finding of pulmonary edema was the first indication of an abnormal retention of fluids in the tissues, although in most instances the dependent portions of the body and the extremities were the first to show edema.

It is obvious that in most instances the development of edema did not per se constitute a grave danger. In several instances, however, it apparently retarded the normal functioning of a gastro-enterostomy and rendered convalescence longer and more unpleasant because of vomiting. It may be that this is a not too uncommon cause of poorly functioning gastro-enterostomies during the immediate postoperative period. In one instance death was undoubtedly caused directly by partial intestinal obstruction due to edema of the intestinal wall. Oxygen therapy was considered necessary in two instances because of extreme pulmonary edema. The avoidance of such postoperative edema is obviously desirable. A limitation of the quantity of fluids and salt administered in cases showing definite malnutrition before operation would seem a logical corollary. In addition, preliminary determinations of serum protein and chlorides would serve as a partial indication for such limitations. In extremely undernourished patients a preliminary gastrojejunostomy might well be advised in order to permit a satisfactory protein intake for some days until the serum protein had

been raised above the critical level. Milk, egg albumin and gelatin are the most easily utilized foods for such a purpose. If intestinal edema develops after a surgical procedure, it may be combated either by attempting to raise the serum protein by limiting the intake of water and salt or alkali, or by producing a diuresis. When it is impossible to feed large amounts of protein, repeated transfusions are of some immediate benefit and should be considered even in the absence of anemia. Transfusion of plasma alone would be the most advantageous, if such a procedure could be carried out. The most efficient methods of producing a diuresis consist in the administration of the mercurial diuretics intravenously, or by the intravenous administration of very concentrated solutions of dextrose. Digitalis is of no value. As all the foregoing measures for the treatment of edema after it has developed demand intensive and sometimes rather heroic action, preventive measures are much to be desired. This is especially true because of the possible avoidance of postoperative complications and a shortening of convalescence, and also because of a possible reduction in operative mortality.

## SUMMARY

1. Data on thirty-four patients who developed a critically low amount of serum protein following routine surgical procedures are presented. Some degree of edema was present in most of them.

2. It is suggested that usually such low values for serum protein and the consequent edema are the result of undernutrition, which may take place both before and after operation. The reduction in the intake of protein is probably the most important element in their pathogenesis.

3. Additional factors in the production of these complications may be the administration of excessive amounts of fluid and salt after operation, especially by the intravenous route, profuse surgical drainage, the general effects of sepsis, loss of serum protein by massive hemorrhage and a retention of base due to temporary disturbance of renal function.

4. The possibility has been noted of the occurrence of edema, even in the presence of apparently normal values for serum protein.

5. The possibility of a nutritional edema of the intestinal wall as a cause of a poorly functioning gastro-enterostomy has been discussed, and the suggestion has been made of the advisability of performing a preliminary jejunostomy for feeding purposes in patients who are obviously undernourished and who require major gastric surgical procedures.

6. The treatment of the complication of postoperative edema has been discussed.

# DIAGNOSIS OF SURGICAL TUBERCULOSIS

## COMPARISON OF DIAGNOSIS BY INOCULATION OF GUINEA-PIGS AND BY CULTURE

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In recent years the use of culture methods for the isolation of tubercle bacilli in the diagnosis of tuberculosis has received considerable attention. Several methods have been proposed for the isolation of tubercle bacilli, the majority being based on procedures designed to eliminate possible contaminants and to supply the peculiar nutritive requirements of the tubercle bacillus. Thus, the methods of Hohn,[1] Petragnani,[2] Miraglia [3] and Loewenstein [4] have been employed in various European laboratories, while the procedures devised by Petroff,[5] Corper and Uyei,[6] Sweany and Evanoff [7] and others have received attention in this country.

Corper and Uyei studied the relative efficiency of various alkalis and acids in destroying contaminants in tuberculous materials. They concluded that acids, as recommended by Loewenstein, were superior to alkalis, and of the former, sulphuric acid gave the best results in their first series of tests. Based on this, they first proposed a method of cultivation of tubercle bacilli from tuberculous materials, which involved treatment of the material with an equal volume of 6 per cent sulphuric acid at 37 C. for thirty minutes, concentration by centrifugation and inoculation of the sediment onto crystal violet-potato slants. Crystal violet, certified by the Commission on the Standardization of Biological Stains, was used as a bacteriostatic agent to inhibit growth of contaminations. A small amount of glycerin broth was placed in the bottom of each tube. Corper and Uyei later found that glycerin water could be

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From the Laboratory Division, Hospital for Joint Diseases.

1. Hohn, J.: Zentralbl. f. Bakt. (Abt. 1) **121**:488, 1931.
2. Petragnani, G.: Atti Accad. fisiocrit. **1**:173, 1926.
3. Miraglia, M.: Pediatria **37**:1167, 1929.
4. Loewenstein, E.: Wien. klin. Wchnschr. **37**:231, 1924.
5. Petroff, S. A.: J. Exper. Med. **21**:38, 1915.
6. Corper, H. J., and Uyei, N.: J. Lab. & Clin. Med. **13**:469 (Feb.) 1928; **14**:393 (Feb.) 1929.
7. Sweany, H. C., and Evanoff, M.: Am. Rev. Tuberc. **17**:47 (Jan.) 1928; **18**:661 (Nov.) 1928; **20**:227 (Aug.) 1929.

used in place of the glycerin broth.[8] They further modified their technic by the substitution of 5 per cent oxalic acid for the sulphuric acid used in the preliminary treatment of the material to be cultured.[9] They reported that when oxalic acid was used, a greater proportion of the tubes inoculated gave growth, and there was an appreciable reduction in the number of contaminations.

The possibilities of the application of the culture method to clinical material led us to institute a comparative study of inoculation of guinea-pigs and the method of Corper and Uyei in the laboratory diagnosis of tuberculosis.

## EXPERIMENTAL DATA

*Technic.*—About two thirds of the specimens used were treated with sulphuric acid, as first described by Corper and Uyei, and one-third with oxalic acid. Our technic, based on that of Corper and Uyei, is as follows:

Five per cent oxalic acid (6 per cent sulphuric acid in the earlier tests) was the reagent employed to destroy contaminants. The potato tubes consisted of the usual potato cylinder slants which had been soaked for from one to two hours in 1 per cent sodium carbonate containing 1:100,000 certified crystal violet. In the bottom of the potato tubes was placed 2 cc. of 5 per cent glycerin water. Equal volumes of the acid reagent and the material to be examined were placed in a 15 cc. centrifuge tube, mixed thoroughly by shaking, and incubated at 37 C. for thirty minutes. Ten cubic centimeters of sterile salt solution (0.85 per cent) was then added; the mixture was shaken and concentrated by centrifugation. Smears of the sediment, stained by the Ziehl-Neelsen method, were always examined before the sediment was cultured or injected into a guinea-pig. It is interesting to note that tubercle bacilli were rarely found in smears of the specimens used. The sediment was inoculated onto four potato slants. The tubes were sealed with sealing wax and incubated at 37 C. Tissues to be cultured were first ground in a Rosenow tissue crusher and suspended in a few cubic centimeters of sterile saline. The suspension was then treated like a fluid specimen, as previously described. The method was used with pus, urine, synovial fluid, tissues, pleural fluid, sputum and feces.

The sediment obtained as described was divided into two portions, one portion being used for culture and the other for inoculation. The guinea-pigs were inoculated subcutaneously in the right axilla. The animals were fed on an adequate diet and kept in individual cages in clean quarters.

After incubation of the cultures for fourteen days without opening, they were examined at intervals of one week, individual smears being made from each tube and stained by the Ziehl-Neelsen method (steaming in fuchsin for ten minutes). As soon as typical acid-fast bacilli were found in one or more smears from a culture, the guinea-pig inoculated with the same material was killed and autopsy performed. If an abscess or necrotic tissue was present at the site of inoculation, smears were made and examined for acid-fast bacilli. Portions of the liver, spleen and lymphatic tissue at the point of inoculation were taken in a diluted solution of formaldehyde, U. S. P. (1:10) for histologic examination. The cultures were

8. Corper, H. J., and Uyei, N.: Simple Glycerol Water-Crystal Violet Potato Cylinder Medium for Diagnostic Cultures of Tubercle Bacilli, Arch. Path. **7**:835 (May) 1929.

9. Corper, H. J., and Uyei, N.: J. Lab. & Clin. Med. **15**:348 (Jan.) 1930.

returned to the incubator, to remain until a satisfactory growth had occurred. As long as cultures were negative on repeated smears, they were examined at weekly intervals for six weeks. If negative at this time, they were held in the incubator for four weeks longer, being examined weekly for visible growth. At ten weeks, after final smears were made and examined, the cultures were discarded, and autopsy was performed on the guinea-pigs. Even though no gross lesions were found at autopsy, the liver, spleen and tissue at the point of inoculation were taken for histologic examination. This is a routine procedure in this laboratory. Only after such examination of cultures and of sections of tissue from the guinea-pigs was a specimen considered to be nontuberculous.

*Results with Specimens from Nontuberculous Cases.*—One hundred and six specimens were studied. These were distributed as follows: synovial fluid, sixty-two; urine, twenty-two; pus, ten; tissue, four; pleural fluid, five; hydrocele fluid, sputum and stool, one each. Of the specimens of synovial fluid, forty-one were from cases of the various nontuberculous arthritides, sixteen from cases of synovitis, two from cases of bursitis and one each from a case of popliteal cyst, a possible endothelioma of the distal end of the femur and a case of osteochondritis dissecans. The twenty-two specimens of urine were from sixteen patients, urine from both the right and the left kidney of six patients being cultured. Eighteen specimens of urine were obtained by cystoscope, and four were specimens from the bladder. The specimens of pus were from various abscesses and sinuses. The tissues represented material taken for biopsy—lymph glands and tissue from joints. The specimens of pleural fluid came from cases of pleurisy with effusion, simple pleural effusion and neoplasm of the lung. All of the specimens used had been sent to the laboratory for routine inoculation into guinea-pigs, in many instances to rule out the possibility of tuberculous infection.

As indicated previously, cultures of these materials were incubated for ten weeks; smears were made weekly for six weeks, and again at ten weeks. Autopsy was performed on the guinea-pigs at the end of ten weeks, and sections of their tissues were studied, before they were considered to be nontuberculous. Final confirmation of the nontuberculous nature of each specimen was obtained by a study of the individual histories, all available diagnostic criteria being taken into consideration.

The results of the culture and inoculation in these one hundred and six parallel tests checked in all except ten cases, in which they were obscured either by the premature death of the guinea-pigs or by accident to the cultures. Five guinea-pigs died of intercurrent infection within a short time after inoculation. In all cases the corresponding cultures were sterile at the end of ten weeks. Of the remaining five instances in which the parallel tests could not be compared, all four tubes in each of three cultures became contaminated from one to four weeks after inoculation. Two other cultures were destroyed at three weeks when a

faulty thermostat caused the temperature of the incubator to rise to 55 C. over a week-end. In these five cases, at the end of ten weeks, gross and histologic examinations of the corresponding guinea-pigs gave negative results.

In summary, therefore, agreement of the results was obtained in ninety-six of the nontuberculous specimens. In ten additional cases one or the other of the two methods failed, so that comparison was not possible. However, in these ten instances presumptive evidence of the nontuberculous nature of the material under examination was obtained by one method, even though the parallel test could not be used for comparison. In no case was the parallel result lost because of the failure of both tests to be carried to completion.

*Results with Specimens from Tuberculous Cases.*—A total of forty-four specimens from forty-two tuberculous subjects was cultured. The distribution of these was: synovial fluid, eighteen; pus, eighteen; urine, six, and tissue, two. Of the specimens of synovial fluids, fifteen were from the knee joints, and one each from the elbow, shoulder and hip joints. The pus was obtained from various abscesses and sinuses, the majority being associated with infections of the bone or joint. Five specimens of urine were obtained by cystoscope; one was a specimen from the bladder. From one patient, urine from both the right and the left kidney was cultured. Both specimens of tissue came from ankle joints.

Thirty-four specimens, from thirty-two persons, yielded cultures of tubercle bacilli. As indicated previously, the cultures were examined by smears of all tubes at weekly intervals until the smears revealed the presence of typical acid-fast bacilli. Twelve cultures were first positive at two weeks, seven at three weeks, six at four weeks, four at five weeks, three at six weeks and one each at seven and ten weeks. In a few cases, at various time intervals from two to ten weeks, the positive smear coincided with the appearance of macroscopic growth, although as a rule the visible growth did not appear until later. A positive diagnosis having been made by smear, the tubes were held in the incubator until a satisfactory growth occurred, when they were placed in stock. For diagnosis, Corper and Uyei waited until macroscopic growth appeared in their culture tubes; in the majority of cases this occurred at about the fourth or fifth week, although at two weeks growth was sometimes visible. It would seem that the earlier examination by smear possesses a distinct advantage in that the time of arriving at a diagnosis is shortened materially, without any appreciable sacrifice of accuracy.

When the cultures were positive by smear, the guinea-pigs were killed and autopsy performed, tissues being taken for histologic examination. Occasionally no gross change was found in the axilla, particularly when the guinea-pig was killed at two or three weeks after

inoculation. Usually there was a small nodule, with or without a caseous center, and in some instances there was only a mass of necrotic tissue, with no focus therein. Smears were made from the necrotic tissue or from an abscess, when present. The smears generally revealed the presence of acid-fast bacilli, but often they were rare and were found only after prolonged search. Abscesses, when present, were small, and sometimes palpable, at the time the animal was killed, but of themselves were not sufficient for diagnosis.

We found that guinea-pigs killed from two to four weeks after inoculation (when the cultures were positive) showed no gross tubercles in the liver or spleen in about half of the instances. Likewise, histologic examination of sections from the liver and spleen was negative for tubercles. Indefinite "tubercle-like" bodies were sometimes reported, but these were not definite enough to make a diagnosis of tuberculosis on the tissues. The diagnosis in these cases was definitely established by the positive culture.

On the other hand, when the cultures first became positive five or more weeks after inoculation, guinea-pigs killed at this time invariably showed gross evidence of tuberculous infection at autopsy, which was confirmed by histologic examination. In all of these, well developed abscesses containing acid-fast bacilli were found at the point of inoculation.

In ten of the tuberculous cases the cultures remained sterile for ten weeks. The corresponding guinea-pigs in five of these showed tuberculosis on gross and microscopic examinations. One was further confirmed when a surgical specimen removed some months later showed the presence of tuberculosis.

In three other cases, inoculation into the guinea-pigs gave negative results for tuberculosis and the cultures were also negative. Aspirated material from three persons with tuberculosis of the knee was used for culture and inoculation. Subsequently, tissue removed surgically from the knee joints of these three patients was shown histologically to be tuberculous, and the clinical course in these cases further confirmed the pathologic diagnosis.

Of still greater interest is a case of tuberculosis of an ankle in a woman 42 years of age. In January, 1929, she developed acute pain with swelling in the ankle, which after six months became more severe. After that, on two occasions, specimens were removed from the tissues of the joint which showed histologically typical tuberculosis. Tissue removed at the second, or fusion, operation was ground in a tissue crusher and prepared by Corper's technic. Cultures made from this prepared specimen were sterile after incubation for ten weeks. Likewise, the liver and spleen of a guinea-pig inoculated with a portion of the same specimen were negative for tuberculosis, grossly and micro-

scopically. However, at the autopsy of the guinea-pig there was a small encapsulated cystic mass in the axilla, containing a milky fluid, in which numerous acid-fast bacilli were demonstrated by smear. Culture of this fluid remained sterile indefinitely. The question arises in this case whether the organisms may not be avirulent for the guinea-pig, the local lesion becoming heavily encapsulated, while they still are capable of producing lesions in human tissues. Furthermore, an artificial environment appears to be unsuitable for their growth.

In this connection, the guinea-pig inoculated with one of the thirty-four positive cultures previously mentioned failed to develop generalized tuberculosis, with involvement of the liver and spleen, after six weeks. However, tubercle bacilli were found in the axillary abscess, which yielded a satisfactory growth on culture. The original culture when inoculated into a guinea-pig killed the animal in thirteen weeks.

Finally, one case is included of a man with a lesion of the lumbar vertebrae, which had all the clinical and roentgenologic appearance of Pott's disease. Two surgical specimens were submitted from the sinus tract, both of which showed chronic inflammation, but no evidence of tuberculosis. In addition, three guinea-pigs were inoculated with pus discharging from the sinus, one of these specimens also being cultured by Corper's method. The cultures and tissues from the guinea-pigs failed to reveal either tubercle bacilli or evidence of tuberculous infection.

Comparison as to agreement of all cultures and inoculations cannot be made in this tuberculous series, because the animals were killed as soon as the cultures became positive. When the cultures became positive within from two to four weeks, the absence of tubercles in the liver and spleen merely indicated the lack of dissemination of the infection, as tubercle bacilli were usually found at the point of inoculation. However, there was actual disagreement of results of the two methods in five instances, in which cultures were sterile after incubation for ten weeks, while gross and histologic examinations of the corresponding guinea-pigs revealed tuberculosis. We have had no instance in which the culture became positive, while the guinea-pig failed to show tubercles in the liver and spleen, or tubercle bacilli in the axilla after six weeks. Furthermore, it is of interest to note that in no instance was it impossible to arrive at a definite final diagnosis because of the loss both of the animal and of the cultures.

*Contamination of Cultures.*—As an important feature of the culture method is the use of reagents to destroy contaminating organisms or to inhibit their growth, mention of the incidence of contaminated cultures in this series is of interest. A total of six hundred tubes, representing one hundred and fifty specimens, was inoculated. One hundred and eighty-five, or 30.8 per cent, became contaminated. In practically every instance the contaminating organism was a mold. We found that the

percentage of contamination occurring in the series treated with oxalic acid was appreciably lower than in the series treated with sulphuric acid. However, it must be remembered that our cultures were repeatedly opened for the purpose of making smears. Only a relatively few of the contaminations which occurred were found when the tubes were first examined at two weeks; thus they represent organisms which resisted the original acid treatment. The majority of contaminations occurred after the tubes had been opened one or more times. Hence we cannot ascribe the apparent difference in degree of contamination of the two series to the preliminary treatment.

In thirty-four cases in which positive cultures were obtained, a total of one hundred and thirty-six tubes was inoculated. Twenty-two tubes, or 16.1 per cent, became contaminated. Nearly 9 per cent of the contaminations occurred before cultures had become positive, and about 7 per cent after they were positive, as revealed by smear. However, these contaminations were so distributed that in nearly every instance two or three tubes remained uncontaminated, in which growth of tubercle bacilli eventually occurred. In only one instance was it impossible to obtain a stock culture, because all the tubes were eventually covered with mold.

The possibility of contamination may be a valid reason for allowing the cultures to remain unopened until a macroscopic growth occurs, rather than incur the risk of losing all cultures by the overgrowth of contaminating micro-organisms. This difficulty might be obviated by adding one or two tubes to each series of inoculations, which would be allowed to remain unopened during the entire period of observation. From our experience, the possibility of obtaining a positive diagnosis at the earliest opportunity outweighs the relatively infrequent loss of cultures because of contamination of all tubes of a series. Such loss by contamination of all tubes occurred fifteen times in our series of one hundred and fifty cases (10 per cent). This is a statistical percentage, however, and does not reveal what actually happened. Fourteen of these cases of loss occurred in the series treated with sulphuric acid, and only one in the series treated with oxalic acid. This is due, we believe, not to the method of preliminary treatment (since the tubes were repeatedly opened), but to the fact that the experience gained in handling the tubes of the first series resulted in the adoption of refinements in technic which yielded definitely fewer contaminations generally in the second series.

## COMMENT

It is frequently important to arrive at a diagnosis earlier than is allowed by the ordinary inoculation of guinea-pigs. Corper and Uyei waited for the development of macroscopic growth in their cultures, which usually occurred in four or five weeks, and occasionally in two

weeks. We have shown that an early diagnosis by culture may be obtained by making smears of the cultures at a time when macroscopic growth has not yet occurred, and when the guinea-pig does not show any signs of tuberculous infection. We found that twenty-five of thirty-four cultures were positive at four weeks or less (twelve were positive at two weeks). On gross and histologic examination at this time, seventeen of the twenty-five guinea-pigs did not show tuberculosis, or at the most the condition was only suspected. When smears are positive, the cultures may be reincubated for the development of visible growth, which furnishes a positive check on the early diagnosis. The possession of cultures makes possible any further work desired, such as type differentiation.

Thus this study brings out the fact that there are two definite advantages in the cultural method of diagnosis. One is that, by weekly examination of smears from the cultures, it may often be possible to make an earlier diagnosis (from two to four weeks) than with the routine guinea-pig method. While this is so with the Corper method, it is quite likely that some other method, particularly one employing an egg medium, would give as satisfactory, if not better, results.[10] The other advantage of the culture method is that, should the guinea-pig die of intercurrent infection, the culture may remain to help establish a final diagnosis. Peculiarly enough, this was the case only with our nontuberculous material, in which five guinea-pigs died of intercurrent infection, while the cultures remained sterile during the entire period of observation.

Mention has been made of the occurrence of palpable abscesses in some of the animals soon after inoculation. While it is true that a lesion was present in the axilla which could be felt, and that tubercle bacilli (although frequently rare) could be demonstrated therein by smear when autopsy was performed, it must be remembered that the mere presence of an abscess in the axilla from two to four weeks after inoculation is not always indicative of tuberculous infection, and not a sufficient reason for killing the animal at this time. We have encountered a number of cases in which such an abscess persisted for some time after inoculation, due presumably to other micro-organisms, which were demonstrable by smears. These abscesses eventually disappeared, and the animals were shown ultimately by histologic section to be non-tuberculous.

On the whole, we feel that inoculation of animals cannot be supplanted by any culture method. In five of forty-four instances in our series (11.3 per cent), the guinea-pigs showed tuberculosis, while their

10. Feldman, W. H.: Am. J. Clin. Path. **1**:285 (July) 1931. Hohn.[1] Sweany and Evanoff.[7]

corresponding cultures remained sterile for ten weeks. The inoculation method itself has many pitfalls, because of a number of factors which are difficult to control. The source of the material used for inoculation is highly important. We have obtained both positive cultures and disseminated tuberculosis in guinea-pigs with as little material as is contained on a swab introduced into a tuberculous focus. On the other hand, it is entirely possible to obtain, as previously indicated, synovial fluid from frank tuberculosis of the knee joint, which failed to produce tuberculosis in a guinea-pig or yield a growth of tubercle bacilli, while the tissue removed at biopsy was unmistakably tuberculous. Even in an open operation of a tuberculous focus, it is obvious that tissue may be removed which histologically will disclose tuberculosis, while another fragment sent to the laboratory for culture and inoculation may rarely contain no viable tubercle bacilli or no organisms sufficiently virulent to infect an animal.

It is striking that by the use of the two methods it was possible to arrive at a definite final diagnosis in all of the one hundred and fifty tests; this would have been impossible had only one of the tests been used exclusively. The use both of inoculation and of culture is to be preferred, since the loss of one may be compensated for by survival of the other test, and, as usually occurs, a check on the results is obtained when both tests are carried on to completion.

An outstanding fact in the discussion of the relative value of inoculation of animals and of the cultural method in the diagnosis of tuberculosis is the lack of agreement of the various writers on the subject. Corper and Uyei [6] believe that the cultural method is equal in efficiency to the guinea-pig test, and suggest that the cultural method may be substituted for inoculation. These conclusions were reached from a study of specimens of sputum and urine from persons with tuberculosis, and of tissues from animals experimentally infected with tuberculosis. Our own experience in handling material from clinical cases, such as are found in an institution in which many persons with bone and joint diseases are treated, certainly does not allow the acceptance of such a broad recommendation. If we were obliged to limit ourselves to but one method, we should prefer the guinea-pig test, on the basis of our present results.

Sweany and Evanoff,[7] with their culture mediums, reported somewhat better results by the cultural method than by the inoculation of guinea-pigs. They advocate the use both of cultures and of inoculation for diagnostic work, on the assumption that some organisms will grow well in cultures, while possessing too low a virulence for guinea-pigs, and that other strains will be pathogenic for animals, but will find the artificial environment of a culture medium unsuitable for growth. However, Feldman [10] also reported slightly better results with the inoculation

of guinea-pigs than with the various culture mediums which he used, namely, those of Corper and Uyei, Sweany and Evanoff, and Miraglia. Similar disagreement of opinion is found in reports of various European authors, some claiming the superiority of inoculation, and others reporting cultures to be at least equal to the guinea-pig tests.

An objection frequently raised to the guinea-pig method is the loss of animals by intercurrent infection. It may be pointed out that in this series only five guinea-pigs were lost for such a reason. In instances like these, the test is almost invariably a failure so far as concerns the arrival at a conclusion regarding tuberculous infection, for the animals usually die within a week after inoculation. Possibly inoculation subcutaneously into the axilla, as was done in this series, reduces the possibility of intercurrent infection. The small number of such infections in this reported series is entirely in accord with our usual results in the ordinary routine of the laboratory. Reasons for this, we believe, are found, not only in the site selected for inoculation, but in the fact that the animals are of a healthy stock, and are kept under good hygienic and feeding conditions.

We have pointed out that a careful examination of smears of the sediment obtained by the Corper concentration method rarely revealed the presence of acid-fast organisms. Since considerable time is often spent on such examinations with negative results, it appears that, for practical purposes, this preliminary examination might be omitted, particularly when applied to synovial fluid.

We make it a practice in this laboratory always to confirm the gross diagnosis on the liver and spleen of the guinea-pigs by histologic examinations of these tissues. Many laboratory workers feel that this is an unnecessary check. Others feel quite the opposite, stating that nontuberculous infections may be mistaken for tuberculosis on gross examination. Our own experience indicates that the gross examination checks satisfactorily with the microscopic. However, in spite of this, we have established the practice of making histologic examinations, since it adds little burden to the routine in a laboratory where tissues are constantly being examined.

## SUMMARY AND CONCLUSIONS

One hundred and fifty specimens (one hundred and six nontuberculous and forty-four tuberculous) were studied in a series of parallel diagnostic tests, inoculation into guinea-pigs and the method of Corper and Uyei of cultivation on crystal violet glycerin water potato medium being used.

With ninety-six nontuberculous specimens, agreement of culture and animal inoculation was obtained. In ten instances no comparison of the results of the two methods could be made—five animals died of intercurrent infection, and five cultures were lost by contamination or accident.

In the tuberculous cases, disagreement occurred in five (11.3 per cent), in which the cultures were negative for tuberculosis, while gross and histologic examinations of the guinea-pigs gave positive results. This shows a definite balance in favor of inoculation of animals.

It was possible to arrive at a definite final diagnosis in all of the one hundred and fifty parallel tests—in the great majority of cases by agreement of both tests, and in a few either by inoculation of animals or by culture, while in no case were both animal and cultures lost. This could not have occurred had only one test been used exclusively.

Thirty-four cultures of tubercle bacilli were obtained from the tuberculous material. An early diagnosis (four weeks or less) was reached in twenty-five of these cases by making smears from the cultures; in these, at the time the smears first showed acid-fast bacilli, the cultures were macroscopically negative, and the guinea-pig at autopsy did not show tuberculosis, or it was only suspected.

While contaminations cannot be avoided, and probably are more frequent when cultures are opened at intervals for smears, the possibility of obtaining a diagnosis at the earliest opportunity appears to outweigh the relatively infrequent loss of all culture tubes of a series by contamination.

At the present time we do not believe that the cultural method should replace inoculation into animals in the diagnosis of tuberculosis. It appears to be preferable, however, to include both methods whenever possible. The one serves as a check on the other, while the double method provides a safeguard against possible loss—by intercurrent infection or contamination.

In the discussion a number of other features are considered concerning the laboratory diagnosis of tuberculosis.

The histologic checking of surgical and guinea-pig tissues was made by Dr. Henry L. Jaffe.

# BACKACHE; LUMBAGO; PAIN IN THE LOWER PART OF THE BACK

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More patients present themselves in the orthopedic department of the Stanford Clinics with backache than with any other complaint. It is frequent in private practice, and is a source of controversy in industrial accident work. Various pathologic entities have been advanced to account for it, some of them purely theoretical and, I believe, erroneous. To treat the symptom scientifically and indeed successfully one must be able to demonstrate definite facts which will account logically for the symptoms and clinical signs. Among the diagnoses which I have discarded as not satisfying these requirements are renal disease, prostatic hypertrophy, neuritis, muscular strain, faulty posture, myositis, fibrositis, fasciitis, radiculitis, rheumatism and pressure on the spinal nerves.

In order to clarify what follows I shall devote a few words to the anatomy of the bones and joints of this region. The bones are the three lower lumbar vertebrae, the sacrum and the two innominate bones.

The bodies of the vertebrae are connected to each other, and the body of the fifth lumbar vertebra is connected to the top of the sacrum, with which it makes a sharp angle, by the thick fibrocartilaginous disks. Between them there is no joint cavity, no synovial membrane. The lateral articulations are true joints, allow a small range of motion and possess a synovial membrane. The plane of the lateral articulation between the fourth and fifth vertebrae, like that of the lumbar articulations above it, is sagittal; that of the lateral articulation between the fifth lumbar vertebra and the sacrum is slightly oblique from the coronal. The coronal set of this articulation prevents the displacement forward of the fifth lumbar, to which its sharp angulation with the sacrum predisposes. The lateral articulations, like any other joints, are subject to sprains, i. e., tears of the capsule. The lateral masses of the fifth lumbar vertebra are large, and in the roentgenogram appear to impinge on the wings of the ilium, but in point of fact normally are separated from it by a good interval, as a glance at the skeleton will show.

The spinal foramina give egress to the spinal nerves, the roots of the sacral plexus. They are of such size and are so placed as to render untenable the assumption that the spinal nerves are ever compromised

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as they pass through the foramina. Indeed, if the spinal nerves ever were pressed on by bone in this situation, extensive and prolonged paralyses would result. These are not seen unless the cord itself is damaged by injury or disease.

The sacrum is wedged between the innominate bones like the keystone of an arch. The sacro-iliac is a true joint lined by irregular fibrocartilage. It possesses a limited range of motion, chiefly of rotation of the ilium. This rotation causes the pubes to move up or down. In heavy lifting, the sacrum is forced down between the ilia, spreading them apart. To demonstrate this, let one place a belt snugly about the pelvis just above the femoral trochanters, and then, bending forward, lift a heavy weight from the ground. If the belt is weak, it will break. Motion in the sacro-iliac joint lessens as age advances, and recent investigations show that in time the joint is often obliterated by bone.

"During pregnancy the pelvic joints and ligaments are relaxed, and capable therefore of more extensive movements" (Gray); hence, probably, the backaches of women during the child-bearing period. The pelvic joints are built for stability, not for mobility. When, during pregnancy, they allow a free motion, they are easily sprained, strained or even, as will be seen later, actually displaced. Of the truth of this statement any one can convince himself by applying a snug belt, *always below the anterior-superior spines of the ilium,* to women who complain of backache during pregnancy and after confinement.

### THE SPECIFIC CAUSES OF BACKACHE

*Arthritis.*—Little need be said here as to the relation of cause and effect. While ideas of treatment may differ, if the clinical signs and the roentgenograms reveal the presence of a lumbar arthritis, the sequence of cause and effect is unmistakable. Let me repeat here that pressure on the spinal nerves plays no greater rôle in causing the pain in inflammation of the spinal joints than in inflammation in the other joints of the body. The cardinal symptoms and physical signs are the same in both, except that the depth of the spinal joints prevents one from observing swelling, heat or sensitiveness to pressure. The pain may be felt in the back alone, or it may be referred down the sciatic distribution. It is a true referred pain. When painful stimuli come in over a certain nerve tract, one refers them to the area from which one is accustomed to receive sensations over this tract, as a man whose leg has been amputated feels pain in his foot. Hence, if I have an inflammation in my lateral articulations, I may complain of typical sciatica.

The importance of the lateral articulations in spinal arthritis has, I believe, been overlooked. They should be studied in anatomic specimens. The roughnesses and irregularities, the "spurring" and "lipping,"

of second type arthritis, so frequently seen, explains adequately the lumbago and sciatica of middle-aged and elderly persons. Indeed, it is possible that these bony changes in the lateral articulations are much more important clinically than are the enormous spikes and ridges of the vertebral bodies on which physicians fix attention.

One thing is important in this connection: No constant relation exists in this type of arthritis between the amount of anatomic change and the clinical picture. A man with a minimal amount of spurring may complain of great pain, while the roentgenograms of the lumbar spine may reveal extensive damage in the joints of a man who does not complain of pain. The characteristic changes are often picked up as an accidental finding in roentgenograms of other organs. These joints, already damaged by the disease, are easily sprained. They are like any other damaged machine. If a man suffers a sudden pain in his back after lifting or falling, and the films show advanced changes in the bone on the same day, they must not be ascribed to the injury.

The treatment of the various forms of arthritis is still a matter of discussion, and I shall not enter into it here at length, but I shall reiterate what I have set forth on numerous occasions. Second type arthritis—degenerative arthritis, hypertrophic arthritis, osteo-arthritis, the arthritis deformans of the Germans, the arthritis characterized by lipping and spurring—is not caused by bacterial infection. All the evidence at one's disposal indicates that the cause is some living organism, not bacterial, which usually gains access to the body through the open bone at the roots of dead teeth. All the changes observed in the bones and joints in this form of arthritis are absolutely different from those caused by bacteria. Further laboratory studies, which I hope soon to publish, confirm the conclusion set forth years ago, that the primary pathologic change is an aseptic necrosis in the bone marrow near the joint. The arthritis which follows, that is, the inflammation in the synovial membrane, is essentially a traumatic arthritis, caused by the distortion of the end of the bone. It follows that any attempts to treat the disease by removal of infection in the tonsil or deep urethra, by the employment of so-called antirheumatic drugs, vaccines and elaborate physical therapy or by attention to the metabolism are doomed to disappointment. The same may be said for operations on the intestinal tract. Even diet is secondary. The supposititious causal organism is probably domiciled in the alimentary canal, and usually the patient with this form of arthritis feels better when his digestive system is in order. Hence he should eat the kind of food which agrees with him. The present fashion of weighing the carbohydrate metabolism reminds one of the Saulsbury treatment with rare beef and hot water, a fad of fifty years ago. A short time ago the important thing was purin metabolism.

One form of treatment which never loses its vogue might be called the ambulatory treatment. It consists in sending the patient to some one else who will cure by diet, irradiation, heat, electricity, massage, or other forms of therapy. Osteopathy, chiropractic and faith healing are on the same basis.

*Fracture.*—Fractures of the spine are often followed by persistent backache, especially if the vertebrae already have been damaged by a preexisting chronic arthritis. The pain may be localized or may be in the form of typical root pain. Sometimes it runs down the thighs as a sciatica. The diagnosis may be made tentatively from the history and from the symptoms and physical signs. A hump may or may not be present. Limitation of motion is the rule. The final diagnosis is established by the roentgenograms.

The most satisfactory treatment is by immobilization. For the milder pains, and especially for elderly persons, a light steel brace is perhaps the best. In younger persons the case is not so simple. Some authorities recommend treatment with a brace, continued for a long time on account of the notoriously slow healing of spinal fractures. I incline strongly to operation in any case of severe persistent pain after fracture, fusing the fractured vertebra with the one above and below it. This puts the damaged piece of machinery out of function. In fact, in any fresh crushing fracture without injury to the cord, in a healthy young person, I always urge operation. This might be regarded as the preventive treatment of backache.

*Spondylolisthesis.*—The acute angulation forward which the spine makes at the sacrolumbar articulation predisposes to the slipping forward of the fifth lumbar vertebra on the sacrum—spondylolisthesis—under stress. A sagittal plane to the lateral articulations also predisposes to the subluxation, as does any destructive osteomyelitis, or rather arthritis. The lesion is rather rare, and occasions persistent backache. The machine here is damaged, out of gear. The joints in the vicinity are strained and sprained when they are used, especially if they are exposed to hard usage. In rare instances the fourth lumbar vertebra slips forward on the fifth.

The only rational treatment for spondylolisthesis is rest. A light steel brace may be worn by the patient as a palliative measure, especially by older persons, but the only curative treatment is to cause by operation a bony ankylosis between the sacrum and the fifth lumbar vertebra. The pain is caused by motion in the distorted joints. It ceases when motion ceases. The actual forward displacement of one bone on the other cannot be corrected, and is of no moment. I speak, of course, of the moderately severe cases showing no damage to the cord, such as are found in patients complaining only of backache. The operation will

tax one's ingenuity if the posterior wall of the proximal part of the sacral canal is lacking.

*Kissing Spines.*—Normally between the spinous processes a distinct interval exists. In certain cases this interval is diminished, and the spines may be brought into contact, or even occasionally overlap. In the roentgenograms a condensation of the bone may be detected on the margin of each spine where it is in contact with the other. A supernumerary joint is thus formed, where it does not belong, and instead of two lateral joints on which the vertebrae swing forward and backward, as on a hinge, the patient has three, arranged as a triangle. Any one or all of these may be sprained, giving a lumbago, a sciatica or both. Some specimens of spinous processes in my possession show cartilage on the margin of the spine, and that the spines are actually in contact

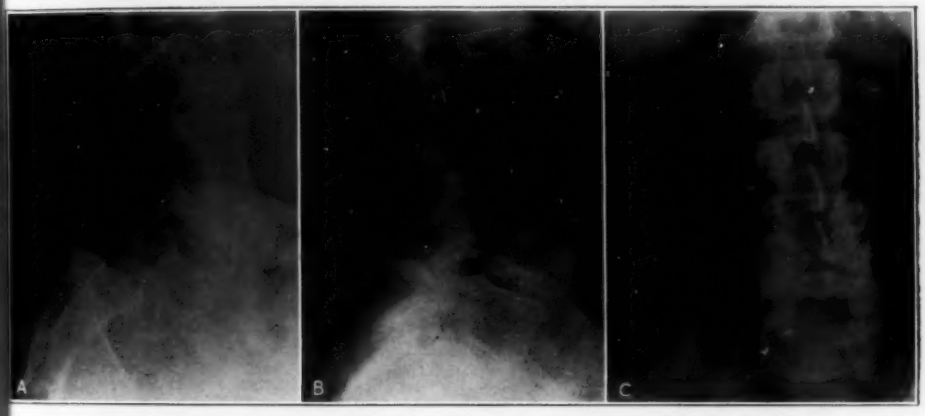


Fig. 1.—*A,* spondylolisthesis, the result of smallpox with spondylitis eight years previously. This caused severe backache and attacks of paralysis. The patient was cured by the insertion of a bone graft. *B,* spondylolisthesis, probably the result of typhoid thirty years previously. Note the evidence of disease in the third and fourth lumbar vertebrae and the spurring of the fifth. The patient has suffered from backache for many years, but won a heavyweight wrestling contest five years after typhoid, and still indulges in hard physical work. *C,* anteroposterior view of the spine shown in *B.* Note the bony bridge between the third and fourth lumbar vertebrae, and the irregularities in the lateral articulations.

can be demonstrated at operation. A joint in this situation is exposed to constant sprain.

This is a comparatively rare cause of backache, but, I believe, a very real one. The physical signs are not clearcut. In spite of the pain, motion, except in extension, is not usually restricted. A list of the trunk may be present. The diagnosis is made by means of the roentgenograms, and is usually missed by the roentgenographer. The possibility of the lesion should be kept in mind.

If motion in the lumbar spine is restricted by a brace, the pain will be lessened, but the only rational treatment is operative. An anklyosing operation may be done on the two vertebrae the spines of which impinge, or better yet, and far simpler, one or both spines may be amputated with a pair of Hibbs bone forceps close to their origin from the arches.

*Congenital Anomalies.*—Apparently the spine in the lumbosacral region is undergoing evolution in the human race. The fifth lumbar vertebra may actually be incorporated with the sacrum, to form a sacral segment, or the first sacral segment may form a part of the lumbar spine

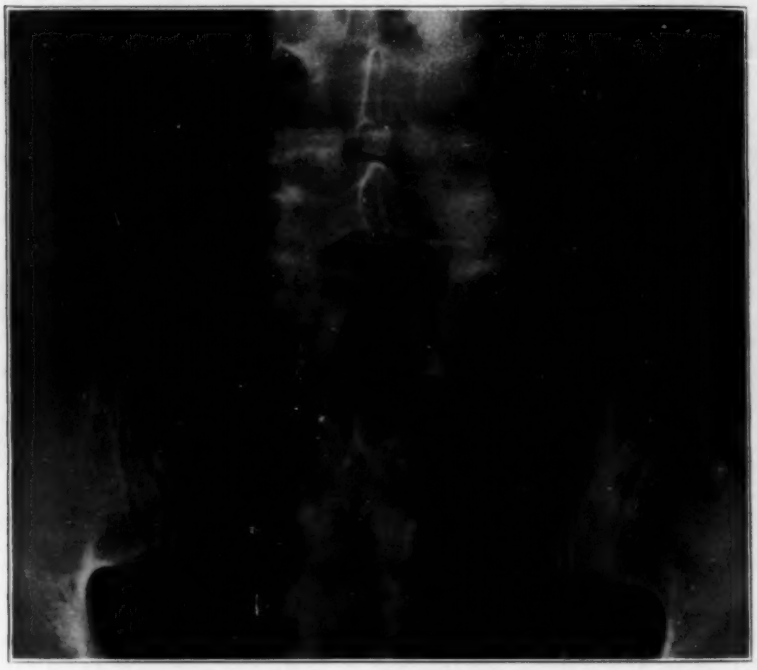

Fig. 2.—Kissing spines. Note the approximation of the spine of the fourth vertebra to that of the fifth, with the squaring and condensation of their contiguous surfaces. The patient was a man of 56, who also had second type arthritis, as determined by examination of a piece of a lateral articulation obtained at a Hibbs' operation.

as a sixth lumbar vertebra. Whether or not the variation constitutes a weakness I do not know.

A change in the plane of the lateral lumbosacral articulations predisposes to spondylolisthesis, as has been noted. Sometimes these articulations are in different planes, sagittal on one side and coronal on the other. Now the machine is out of gear. It is easily injured, as any other machine would be which did not work smoothly. The joints are

strained and sprained. Backache is common, and is frequently quite severe. Strangely enough, in this case, as in the other congenital anomalies, the backache rarely makes its appearance until the third decade of life. The tissues seem to be elastic enough to adapt themselves to the condition until that period.

Variations in the size and shape of the lateral processes are frequent. They may vary in size on the two sides, without causing symptoms, but when one of them is incorporated with the first segment of the sacrum,

Fig. 3.—Low power photomicrograph of a piece of one of the spines shown in figure 2. Cartilage cells appear in the fibrous tissue close to the bone, and between them and the bone is a strip of calcified fibrous tissue.

or is so large and of such a shape as to articulate with the sacrum or with the ilium, this portion of the spine, viewed as a machine, functions badly. It is exposed to strains. Its joints are frequently sprained. They become repeatedly the seat of a traumatic arthritis. Pain is felt in the back and, as in the other lesions in this vicinity, is referred down the sciatic distribution. If the two lateral processes are enlarged symmetrically and articulate with the pelvic bones, the presence of the extra

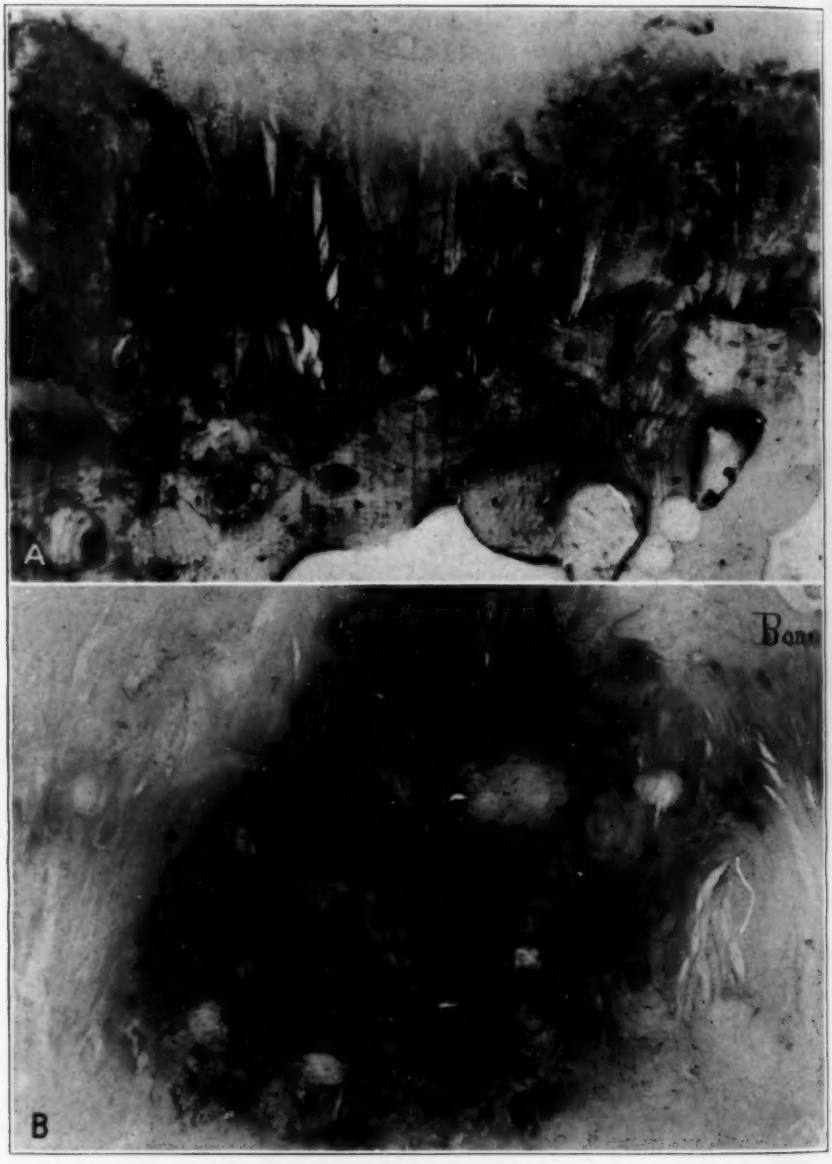


Fig. 4.—*A*, low power photomicrograph of a piece of a spinous process removed from another patient. Note the layer of calcified fibrocartilage adjoining the bone. *B*, low power photomicrograph of a piece of a spinous process removed from another patient. Most of the field is occupied by a calcified area of necrotic tissue. In the fibrous tissue between it and the bone appear cartilage cells.

joints must predispose to injury, to traumatic arthritis. In any of these conditions one can establish with the roentgenograms a definite anatomic fact which can explain the symptoms of which the patient complains.

On the other hand, asymmetry in itself is no cause of backache, provided that the joints are not sprained. The roentgenograms show all sorts of distortions and changes in the shape of the vertebrae in scoliosis, for instance, and the patient may suffer no pain whatever. This makes one suspicious of such vague terms as "static joint diseases" (Preiser), "balance" or "posture." In this connection the reader is referred to an excellent paper by the late Robert Patek of the Stanford

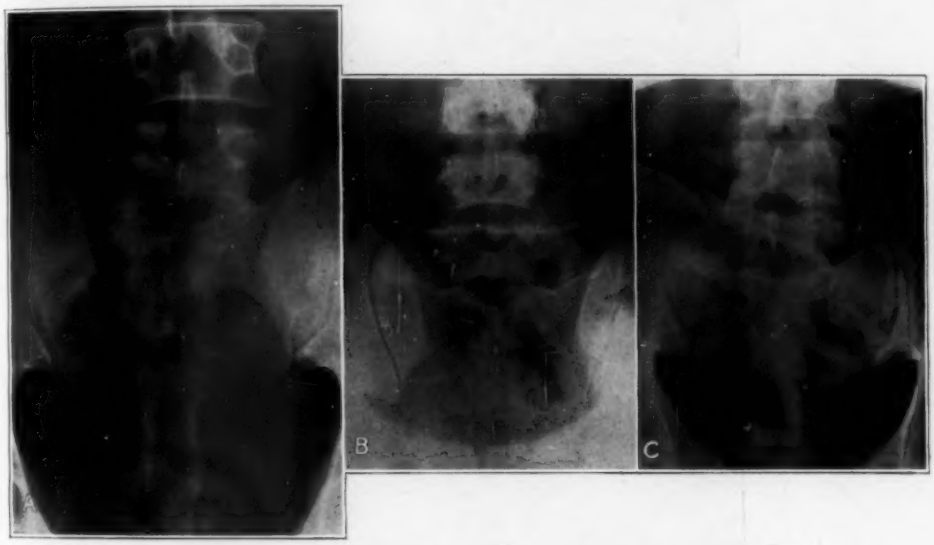


Fig. 5.—*A*, lateral articulations between the fifth lumbar vertebra and the sacrum are in different planes, sagittal on one side and coronal on the other. *B*, congenital anomaly of the fifth lumbar vertebra. Large lateral processes articulate with the sacrum, and on one side probably with the ilium. *C*, congenital anomaly of the fifth lumbar vertebra. The large lateral process on one side articulates with the sacrum.

Clinic, which has not received the attention it merits, perhaps because it contained little of theory and much of fact.[1]

One's chief efforts in these cases are to be directed to limiting motion in the lumbosacral region, and hence to protecting the joints from sprain. The required restraint may be furnished by a light steel brace, or an operation may be necessary. Perhaps the simplest way out is to ankylose

1. Patek, Robert: Static Deformities as a Factor in the Production of So-Called Hypertrophic Arthritis, J. Orthop. Surg. **19**:324, 1921.

the fifth lumbar vertebra to the sacrum. Some operators advise the amputation of a large winglike lateral process on the fifth lumbar vertebra, but the operation is difficult and bloody, and carries a heavy danger of injury to the spinal nerve roots. The other operation is easier and eminently satisfactory.

Without the same definite relation of cause and effect—and I therefore hesitate to include it here—is the backache suffered by persons who lack a proper range of dorsal flexion in their ankle joints, that is, whose

Fig. 6.—Congenital anomaly of the first sacral segment. It forms a sixth lumbar vertebra with a large lateral process on one side, articulating with the sacrum itself.

calf muscles are short. In cases of persistent backache, for which no other cause can be found, I suggest this comparatively frequent deformity be sought. In the milder cases, high heels suffice for treatment. In severe cases, the tendo calcaneus should be lengthened.

*Lesions of the Sacro-Iliac Joint.*—Infectious arthritis is a comparatively frequent cause of backache. With this backache a persistent sciatica is associated. Sensitiveness over the joint is present, and, especially in tuberculosis, sensitiveness over the anterior aspect of the

joint, with infiltration, can be detected by palpation with the finger in the rectum. With this disease the patient will limp, and his trunk in standing will exhibit a lurch away from the affected side. The lumbar muscles show the characteristic spasm, and motion in the lumbar spine, especially flexion, is decidedly limited. The roentgenograms confirm the diagnosis. The only known satisfactory treatment of sacro-iliac tuberculosis is operative ankylosis. With any other treatment the outcome is practically invariably fatal.

Fig. 7.—Tuberculosis of the sacro-iliac joint.

*Sacro-Iliac Displacement.*—Under this and various other names—sacro-iliac slip, sacro-iliac sprain, sacro-iliac subluxation, pubic subluxation, rotation of the innominate bone—a lesion has been described which has occasioned a great amount of controversy. The existence of any such lesion has been disputed. A glance into the past may help one to understand the matter.

Older physicians will recall the standard treatment for sciatica. It consisted in "stretching the sciatic nerve." This was supposed to free it from inflammatory adhesions. Under narcosis the thigh on the

affected side of the supine patient was flexed to a right angle, and then the leg was forcibly extended, the so-called Kernig manipulation. Sometimes the flexion of the entire extremity was carried to such an extent that the foot approached the patient's face. Paralysis of the sciatic nerve has been caused in this way. This was the so-called dry stretching. If the manipulation were not successful, bloody stretching was done at a later time. The sciatic nerve was exposed in the back of the thigh, and the delicate connections of the nerve with the tissues in which it lay were identified as adhesions. The operator then hooked his first and second fingers under the nerve, separated the "adhesions" throughout the extent of its exposed portion and then stretched the nerve by almost lifting the patient from the table. In spite of the absurd theory on which these operations were done, the fact that they often were successful appeared to justify it.

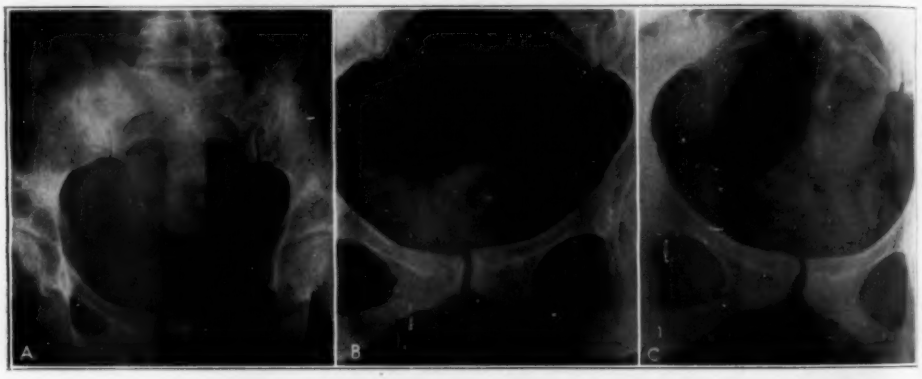


Fig. 8.—*A*, pubic subluxation; rotation of the innominate bone. This picture was taken with the patient prone. It shows the pubes slightly higher on the right. *B*, this picture of the same patient, standing with her weight on the right foot, shows how the displacement is increased. *C*, in this picture the patient stands on her left foot, and the displacement disappears. *A*, *B* and *C* present the classic pictures of this lesion. When the rotation has been corrected by manipulation, these displacements are not obtained.

About twenty-five years ago a reformed osteopath, studying medicine at Harvard Medical School, interested the orthopedic staff in the subject of slip of the sacro-iliac joint as a cause of lumbago and sciatica, and precipitated a controversy which has endured to the present. The treatment recommended was essentially the same as that for stretching the sciatic nerve, except that for bloody stretching was substituted simple forced superextension of the thigh on the body.

A fairly definite symptomatology was built up for the lesion. As a rule, the onset was sudden. The patient, while lifting or straining, felt a sudden pain in the region of the sacro-iliac joint, which often ran

down the sciatic distribution. This often completely incapacitated him. All motions in the lower part of the spine were impossible, the lumbar muscles were in spasm and the trunk was drawn over to the side. The Kernig sign was strongly positive. Sensitiveness of the sacro-iliac joint to deep pressure was present, but the patient did not limp.

The treatment outlined usually was successful, when care had been used in the diagnosis. Often during the manipulation a slight click could be felt, or even be distinctly heard by bystanders. However, the fact that no displacement could ever be detected by roentgenograms cast doubt on the correctness of the diagnosis. About ten years ago Dr. H. R. Allen of Indianapolis advanced the idea that the displacement of the sacro-iliac joint was not up or down, but was simply a fixed rotation of the ilium on the sacrum, and that the place to look for its manifestation was not at this joint but at the symphysis pubis. As Dr. Allen expressed it tersely, if one wanted to the tell the time, one would not look at the center arbor of the time piece around which the hands move, but out at the ends of the hands. This was done, the fixed displacement was identified at the symphysis pubis and for many the problem was solved. Unfortunately, the idea does not seem to have attracted much attention. It explains well how treatment hitherto carried out on an erroneous theory was nevertheless successful.

The displacement of the pubes is usually upward on the affected side. If, then, the usual first maneuver of replacement is tried—the forced Kernig maneuver, dry stretching of the sciatic nerve—the hamstring muscles, attached to the tibia and to the ischial tuberosity, will pull the os innominatum in such a way as to increase the displacement. "Dry stretching" of the sciatic nerve will not cure the condition. If the patient is turned on his face, and if his thigh is then superextended, by simple manipulation, or after incision and "freeing of sciatic adhesions," the Y ligament will pull the pubes downward and reduce the displacement.

Occasionally the displacement of the pubes is downward, on the affected side. Then the forced Kernig manipulation will reduce it.

Here then is a set of symptoms and clinical signs perfectly compatible with a diagnosis of a sprain of the sacro-iliac joint. Roentgenograms of the symphysis pubis show an anatomic condition capable of explaining the sacro-iliac sprain. When the displacement of the pubes is corrected, as shown roentgenologically, the symptoms and physical signs disappear, leaving perhaps only a slight feeling of soreness. If the clinical picture presents itself again, the procedure can be repeated. It should not be necessary to add that the simple manipulation here described would not cure an inflammation of the sciatic nerve, a fibrositis, a myositis, a fasciitis, a radiculitis or the results of pressure on a spinal nerve.

*Neoplasms.*—Malignant bony growths can cause an agonizing backache, for which nothing but narcotics can be prescribed. Their presence should always be suspected, particularly in persons suffering from malignant growths elsewhere.

## CONCLUSION

I have detailed lesions of the motor apparatus which can be established as a reasonable cause for the backaches seen in the clinic and in private practice. In the treatment of this symptom one should rely on facts rather than on theories. In diseases and injuries of bones and joints one must adopt the methods of modern medicine. One must discount the extravagant claims of cure made by the advocate of some peculiar means of treatment, and must demand some concrete evidence of the truth of his claims. Here as elsewhere in medicine one's ideas must be based on the correlation of sound pathologic observation, clinical evidence and experiment.

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# BONE AND CALCULI IN THE COLLECTING TUBULES OF THE KIDNEY

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CHICAGO

In this paper the occurrence of bone in the human kidney in close association with parenchymatous stones will be described and its bearing on the theory of osteogenesis pointed out.

The occurrence of bone in the kidney under experimental conditions has attracted much study since the original demonstration by Sacerdotti and Frattin [1] (1901). It had long been demonstrated that following ligation of the renal artery or artery and veins, there occurs a massive necrosis of the renal substance, but not of the renal pelvis and ureter because of a different vascular supply. Extensive calcification of the necrotic renal tissue occurs within a few days (Blessig [2]), and bone [1] develops some weeks later, forming chiefly and constantly beneath the mucosa of the pelvis with spurs extending into the remains of the kidney. The demonstration [3] of a bone-stimulating effect of the epithelium of the renal pelvis makes it probable that this was the cause of the bone formation in the experiments of Sacerdotti-Frattin, especially since it does not occur if the epithelium of the pelvis dies, for example, as a result of ligation of the ureter and the renal artery simultaneously.

Bone formation in the kidney in man associated with renal calculi was first demonstrated by Phemister,[4] who observed it in three instances in two patients. In each instance living spongy bone with fibrous and fatty marrow occurred in a pedunculated mass of fibrous tissue attached to the renal pelvis and partly surrounded by stone. The inorganic portion of the stone was mainly calcium oxalate, with lesser amounts of calcium carbonate and phosphate. A similar kind of bone asso-

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From the Department of Surgery of the University of Chicago.

1. Sacerdotti, C., and Frattin, G.: Ueber die heteroplastische Knochenbildung, Arch. f. path. Anat. **168**:431, 1902.

2. Blessig: Ueber die Veränderungen der Niere nach Unterbindung der Nieren Arterie, Virchows Arch. f. path. Anat. **16**:120, 1859.

3. Huggins, C. B: Influence of Urinary Tract Mucosa on the Experimental Production of Bone, Proc. Soc. Exper. Biol. & Med. **27**:349, 1930; The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, Arch. Surg. **22**:377 (March) 1931; Transplantation of Ureteral Segments to the Abdominal Wall, Proc. Soc. Exper. Biol. & Med. **28**:125, 1930.

4. Phemister, D. B.: Ossification in Kidney Stones Attached to the Renal Pelvis, Ann. Surg. **78**:239, 1923.

ciated with renal calculi occurring in pedunculated masses in the renal pelvis and in part beneath the epithelium of the pelvis has recently been described by Hellström.[5]

Partial replacement by bone of calcified areas in tuberculosis of the kidney, hypernephroma[4] and dermoid cysts of the kidney[6] has been observed.

A different type of bone formation in the human kidney, comparable to the Sacerdotti-Frattin experiment, was recently described by Schmorl.[7] Complete infarction of the blood supply of the kidney occurred with subsequent formation of bone beneath the mucosa of the pelvis. This is the only example of its kind in the literature.

Bone occurring under still different conditions was recently observed in the histologic examination of two human kidneys extirpated because of renal calculous disease. In the first case the bone was of a size easily visible to the unaided eye; in the second, it was of microscopic dimensions.

## CASE REPORTS

CASE 1.—*History.*—A man, aged 41, entered the University of Chicago Clinics complaining of left lumbar colic radiating to the groin, of four years' duration. Pus had been present in the urine for at least a year, and a stone had been passed on five occasions. Roentgenograms of the region of the kidney demonstrated rapid growth in the size of the stone in the last six months. Slight pain in the loin was elicited on palpation. The urine contained a moderate number of leukocytes and erythrocytes, found on cystoscopy to be coming entirely from the left kidney. The left kidney was found infected with Staphylococcus aureus. Left nephrectomy was done. Roentgenograms of the excised kidney before and after injection of sodium iodide showed in the lower pole in addition to other shadows a crenated shadow of the density of calcium (figs. 1 and 2) which was the bone described in detail under gross pathologic examination.

*Gross Pathologic Examination.*—The kidney was symmetrically enlarged and weighed 190 Gm. The capsule stripped readily. The pelvis contained 30 cc. of purulent urine, two large and many small calculi. In the lower pole of the kidney was a calcified mass about 0.5 by 0.5 by 0.3 cm. situated in one of the renal papillae and densely adherent to its surroundings. This was excised in situ, fixed in formaldehyde, placed in 5 per cent nitric acid for seven days, and sectioned in paraffin.

*Microscopic Examination.*—This last mentioned calcified area was composed chiefly of spongy bone, and to a much less extent of stone. It was situated in the parenchyma of the kidney in one of the collecting tubules; most of the epithelium lining the tubule had disappeared, but in several areas the cuboidal epithelial lining had been well preserved and served to identify the tubule. There was a cleft (fig. 3) separating the calcified mass from the wall of the tubule and the renal medulla, in places interrupted by fibrovascular invasions entering the bone, carrying

5. Hellström, J.: Ein Fall von metaplastischer Knochenbildung in der Niere in Zusammenhang mit Nierenstein, Ztschr. f. Urol. **25**:401, 1931.

6. Pick, Ludwig: Personal communication.

7. Schmorl, G.: Verhandl. d. deutsch. path. Gesellsch. **25**:190, 1930.

Fig. 1 (case 1).—Roentgenogram of excised kidney containing many calculi and bone. The bone is the crenated shadow (*A*).

Fig. 2 (case 1).—Renal pelvis injected with sodium iodide. The bone is opposite the arrow.

its blood supply. The bone was cancellous in structure, containing fibrous and fatty marrow. The bone lacunae were filled for the most part with typical living bone cells with easily demonstrable canaliculi (fig. 4).

An interesting relationship existed between the bone and the calculous material. In each of the sections containing bone, the matrix of the inorganic calculus might be seen, but more in the juxtapelvic than in the deeper lying areas of the bone. In the former areas, the margin of the bone was nearly surrounded by the

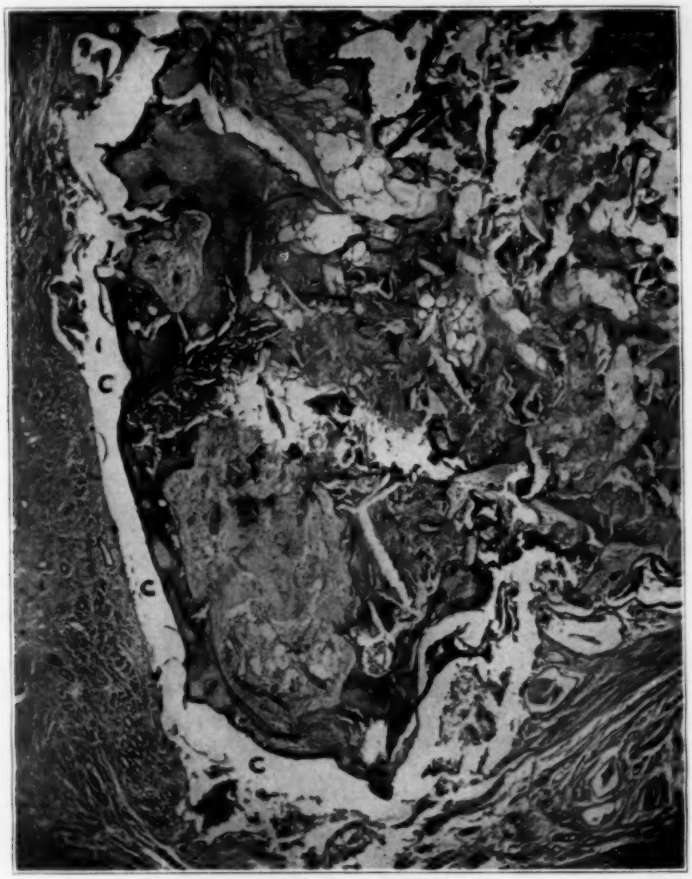


Fig. 3 (case 1).—Photomicrograph showing approximately two thirds of the extent of the bone in the kidney; × 25. Note cleft (*c*) between the calcified mass and the parenchyma.

concentrically laminated, escalloped stone which near the periphery contained a continuous band of a heavily pigmented, brown amorphous material differing widely from the rest of the stone (fig. 5). The stone was easily recognized and presented a concentrically ringed, acellular form, staining deeply blue with hematoxylin. The concentric laminations of the stone were visible only at the periphery of the bone. The center of the bone was occupied in part by crystalline and amorphous

stone material, presenting irregularly curved and angled spaces. In places this material had disappeared, leaving only empty clefts of bizarre shape, mostly with acute angles (fig. 5).

In many places the laminated, acellular stone merged with the living bone in an unmistakable manner, and the bone seemed to have been molded in the form previously occupied by the stone (fig. 6). There was thus no distinct boundary between the bone and the stone in these locations.

Fig. 4 (case 1).—Photomicrograph showing the bone lacunae and canaliculi; × 325.

Otherwise, sections taken through the renal substance in several places showed essentially normal appearing glomeruli, a few of which were undergoing calcification. There were numerous areas of lymphocytic infiltration throughout the parenchyma of the kidney. In several locations in the pyramids calcareous, concentrically laminated calculi might be seen in dilated tubules of the renal papillae (fig. 5 *C*).

CASE 2.—*History.*—A woman, aged 30, entered the University of Chicago Clinics complaining of a constant sharp pain in the left loin, of one week's duration. Previously well, she developed six weeks before a mild acute respiratory infection accompanied by vague abdominal discomfort and constipation lasting the greater part of five weeks; recently left renal colic developed. There were no urinary symptoms. Examination disclosed tenderness in the region of the left kidney. The urine at first examination was normal; later it contained many polymorphonuclear

Fig. 5 (case 1).—The margin of the stone, showing the escalloped edge, heavily pigmented brown band (*A*) and bone (*B*), and containing irregularly shaped clefts; × 80. A microlith is seen at *C*.

leukocytes. Roentgen examination showed many diffuse radiopaque spots in the region of the left kidney with a shadow of a ureteral stone opposite the spine of second lumbar vertebra. Cystoscopy demonstrated lack of function from the left kidney and an impassable obstruction in the upper ureter. Exploration of the kidney showed an impacted stone in the upper ureter, but no free stones in the

renal pelvis; the renal papillae were loaded with small calculi. Complete removal of all the calculi was impossible except by nephrectomy, which was done.

*Gross Pathologic Examination.*—The kidney was moderately enlarged and edematous and weighed 240 Gm. The fibrous capsule stripped easily. A stone was found impacted 1 cm. below the ureteropelvic junction. The renal pelvis was lined with a hemorrhagic, swollen mucosa, and contained no stones. In each of

Fig. 6 (case 1).—An area where direct union may be seen between the laminated stone (*S*) and bone (*B*); × 85. This direct invasive replacement of the stone by bone was seen in many areas in the sections.

the papillary regions of the renal pyramids, a collection of small, hard, black stones, some as large as 0.5 cm. in diameter was found. These areas were excised for microscopic examination. Chemical analysis of one of the stones showed: nitrogen, 1.1 per cent; tertiary calcium phosphate, 10.4 per cent; calcium as oxalate, 75.8 per cent; unaccounted for, 12.7 per cent. Culture from the renal pelvis was sterile.

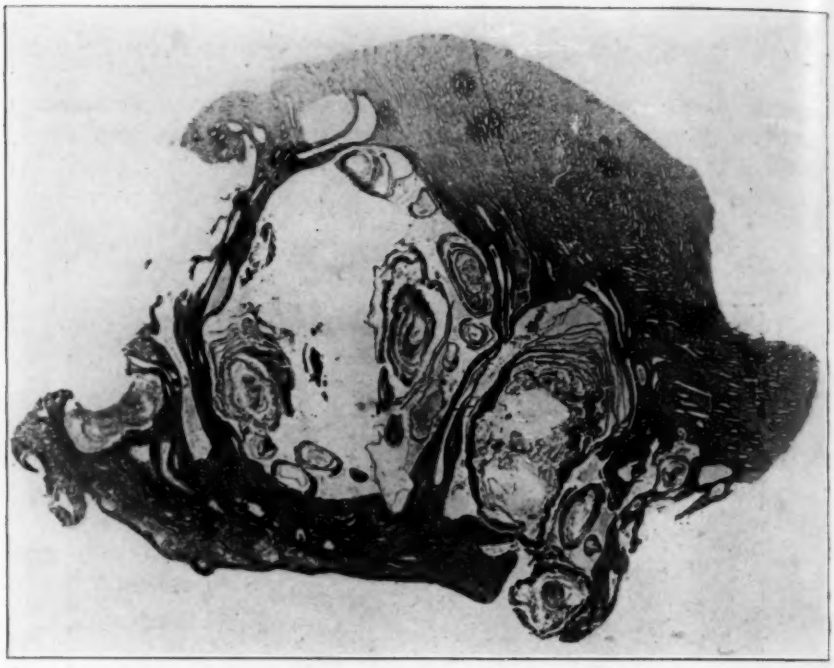

Fig. 7 (case 2).—Longitudinal section through pyramid showing calculi in collecting tubules; × 10.

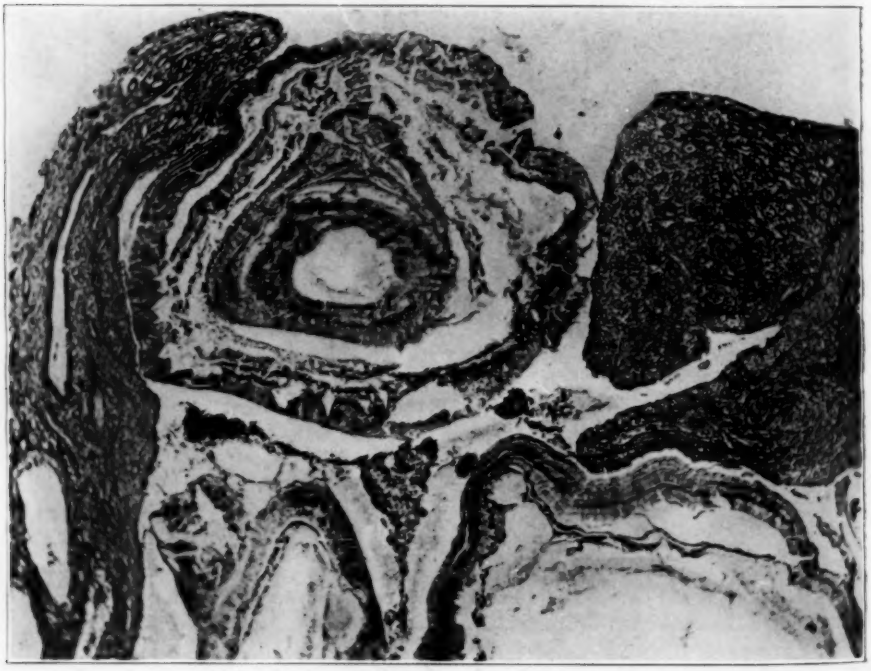

Fig. 8 (case 2).—Photomicrograph showing microliths in the renal papillae, one of which is presenting at the mouth of the tubule; × 50.

*Microscopic Examination.*—Moderate edema of the renal parenchyma was seen with slight extravasation of blood and collections of leukocytes, especially beneath the pelvic mucosa. There was a protein exudate in many of the tubules and moderate dilatation of some of the convoluted tubules.

The chief interest centered in the papillae, where most of the collecting tubules were dilated, some tremendously, with thinning of the epithelium in places. Many of these tubules were filled with calculi (figs. 7 and 8), which were concentrically

Fig. 9 (case 2).—Photomicrograph showing the fibrous nature of the matrix and the bone lacunae, some of which are empty; × 1,500. The insert shows detail of the bone cells.

laminated, took hematoxylin well, and had a granular, amorphous nucleus. Several of these calculi were adherent to the tubular wall, and in one location a calculus was being invaded by connective tissue.

In one set of more than twelve consecutive secretions of these stone-bearing papillae, there was seen a calculus the concentrically layered periphery of which nearly surrounded a homogeneous pink-staining mass of bone. The bone was

attached at one point to the parenchyma of the kidney, and fibrous tissue might be seen entering it. Many of the lacunae were empty, but some contained typical bone cells. The matrix was seen under higher magnification to be fibrous (fig. 9). No direct continuation with the stone as in case 1 could be seen.

### MICROLITHS IN THE KIDNEY TUBULES

As mentioned, small concentrically laminated calculi were found in the lumen of the renal-collecting tubules in these two cases so that a brief consideration of this phenomenon is germane to the present

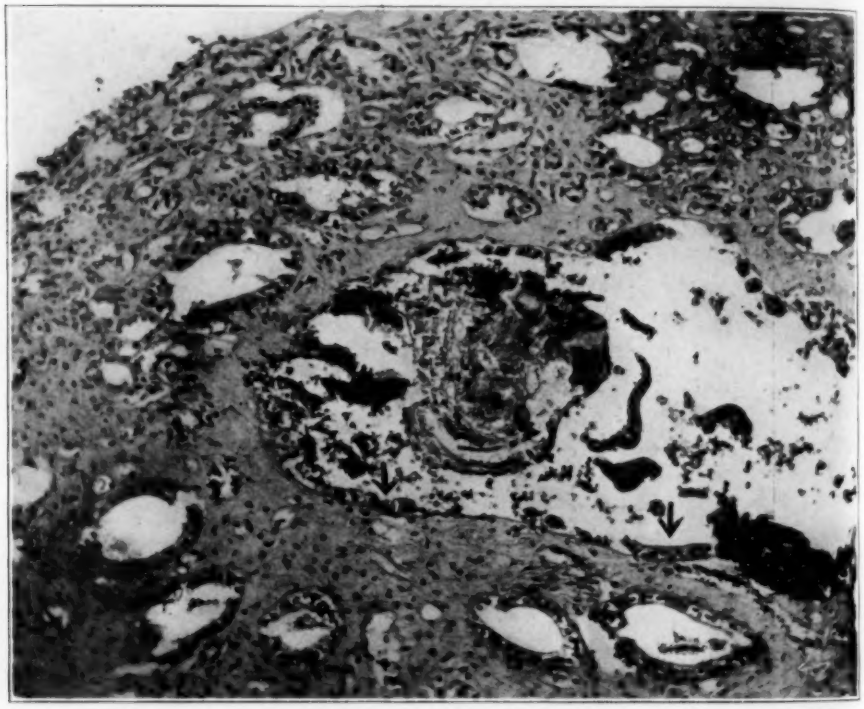

Fig. 10.—A typical laminated microlith from the collecting tubule of a kidney excised because of a coral calculus; × 100. The cuboidal epithelium of the tubule may be seen opposite the arrows.

discussion. These calculi have occasionally been found in the tubules of the human kidney as well as in lower animals. They are distinguished from all other calcium deposits in the kidney by their lamellar arrangement and by their free position in the tubule. They have varied in our experience from purely microscopic dimensions to a size of 1 by 0.5 by 0.5 cm., and doubtless at times are larger. They must be differentiated from calcium infarcts occurring outside the tubules in the

pyramids and the closely related structures described by Lichtenstern,[8] who described calcified deposits attached to the renal parenchyma projecting into the lumen of the tubules. The relation of these small calculi to calcified cylindroids [9] is unknown but may be close.

These microliths have been observed in many of the cases in which kidney stones have been experimentally produced. These include calculi forming (1) after the feeding of the oxamide;[10] (2) after intravenous injections of uric acid and some of its constituents;[11] (3) after intravenous oxalates,[12] and (4) in vitamin A deficiency.[13]

In the adult, renal microlithiasis has been mentioned by Braasch [14] and briefly described by Crabtree.[15] Microliths composed of laminated deposits of uric acid, the uric acid infarcts, are frequently seen in the collecting tubules of infants dying in the first weeks of life, and are known to every pathologist.

In this laboratory, laminated calculi in the tubules in adults have been found in four of sixteen kidneys excised for calculous disease. It has been our experience that unless serial sections of the renal pyramids are made they are easily overlooked; they have not been found where there has been much necrosis of the papillae from the pressure of a coexisting hydronephrosis or from infection. They have been found only in the collecting tubules. It is our feeling that these surgically inaccessible bodies may be a source of recurrence of calculi after conservative operation.

There is also evidence that these structures are closely related to the development of grosser calculi found in the renal pelvis. The evidence may be summarized thus: (1) clinical cases such as case 2, in which one of the calculi obviously passed out of the renal papilla and caused complete ureteral obstruction; (2) the fact that these microliths have the same nucleus formation and concentrically lamellar arrangement as the gross calculi and must adsorb or cause precipitation of similar

8. Lichtenstern, R.: Mikrolithiasis, Wien. klin. Wchnschr. **39**:1156, 1926.

9. Lubarsch, O., in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, p. 564.

10. Ebstein, W., and Nicolaier, A.: Ueber die experimentelle Erzeugung der Harnsteinen, Wiesbaden, J. F. Bergmann, 1891.

11. Heidenhain: Arch. f. d. ges. Physiol. **9**:23, 1874. Ebstein, W., and Nicolaier, A.: Virchows Arch. f. path. Anat. **143**:337, 1896. Minkowki, O.: Arch. f. exper. Path. u. Pharmakol. **41**:375, 1898.

12. Ebstein, W., and Nicolaier, A.: Ueber die Wirkung der Oxalsaure und einiger ihrer Derivate auf die Nieren, Virchows Arch. f. path. Anat. **148**:366, 1897. Keyser, L. D.: The Mechanism of the Formation of Urinary Calculi, Ann. Surg. **77**:210, 1923.

13. Van Leersum, E. C.: Vitamin A Deficiency and Urolithiasis, J. Biol. Chem. **76**:137, 1928.

14. Braasch, W. F.: Unusual Types of Urinary Lithiasis, J. Urol. **23**:1, 1930.

15. Crabtree, E. C.: Tr. Am. A. Gen.-Urin. Surgeons **23**:17, 1930.

isomorphic crystals in a highly saturated solution of the difficultly soluble salts of which they are composed; (3) frequent occurrence of the microliths in experimental lithiasis, and (4) two experiments which may be recounted briefly.

EXPERIMENT 1.—Three groups of three albino rats were fed oxamide by mouth in quantities of from 1 to 3 Gm. daily for one, two and three days, and then killed. In two of three rats killed at forty-eight hours, no gross stones were found in the urinary tract, but crystalline deposits were found in the collecting tubules on histologic examination. In the rats killed at three days, gross calculi were found accompanied by crystalline deposits and microliths in the collecting tubules.

EXPERIMENT 2.—Oxamide was fed by mouth to five albino rats in approximately 1 Gm. amounts daily for seventeen days and then discontinued. The animals were sectioned thirty-three days later. One rat had bilateral pelvic calculi and another had a stone impacted in a ureter. In three rats no calculi were found, and sections of the kidney showed no parenchymatous microliths. In four rats similarly treated and killed at seventeen days as controls, there were massive deposits of oxamide in the collecting tubules as well as elsewhere in the urinary tract.

These simple experiments show, first, that the deposition of concentrically laminated formations of oxamide is the first evidence of the formation of calculi composed of oxamide in the rat; and secondly, that unless the action of the stone-forming agent persists, these bodies are liable to be discharged from the collecting tubules, so that examination at a later date would give no clue to the fact that there had originally been calculi in the renal tubules.

## COMMENT

In the previously reported cases of ossification in the human kidney, the bone was found in close association with the pelvis, whereas here the bone was in the parenchyma of the kidney. The origin of the bone is of interest from a theoretical standpoint. Search was made for areas of mucosa of the renal pelvis in this area, but none was found in close association with the bone, so that it was necessary to discard the idea that the bone arose as a result of an epithelial stimulus.

The bone in each case was in immediate proximity to stone formation, and there were many locations where direct union occurred between the bone and stone (fig. 6). This is considered strong evidence that the bone formed in a somewhat similar way to the histologic picture [16] of creeping substitution in which there is invasive replacement of aseptic dead bone by new living bone. The point of greatest theoretical interest is that in the present cases the process is a creeping

16. Axhausen, G.: Knochennekrose und Sequesterbildung, Deutsche med. Wchnschr. **40**:1 and 111, 1914. Phemister, D. B.: Repair of Bone in the Presence of Aseptic Necrosis, J. Bone & Joint Surg. **12**:769, 1930.

substitution of stone by bone. This is considered good evidence that accumulation of difficultly soluble calcium salts can provide a stimulus for bone formation in certain connective tissue.

As Phemister and Hellström emphasize, it is probable that bone formation in kidneys containing calculi occurs more frequently than the literature indicates.

SUMMARY

1. A type of bone formation in the human kidney located in the medulla in association with calculi in the collecting tubules is described.

2. It is most probable that the calculi served as the stimulus for bone formation. Creeping substitution of stone by the bone is demonstrated.

3. The presence and significance of these intratubular calculi are discussed.

# RELATION OF TRAUMA TO RUPTURE OF HOLLOW ABDOMINAL VISCERA

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Many patients who suffer from various diseases of the intra-abdominal organs attribute the onset of their trouble to a strain or other abdominal injury. Frequently in such cases the attending physician agrees with the theory of traumatic etiology. The result is, when the circumstances permit, a claim for damages or compensation. There is hardly a disease of the abdominal viscera that has not been the subject of personal injury litigation. The claim of traumatic rupture of gastric or duodenal ulcers is a common example. Claims have been made in cases of this kind in which either an alleged or a real injury has preceded the rupture by from a few hours to several days.

Several cases of this kind have come under my observation, and I have always felt that the laws of hydromechanics apply to the abdomen and its fluid contents. However, there is no proof that the laws of fluid pressure in living elastic cavities are the same as those determined for rigid, nonliving containers. Moreover, I could find no reference to the behavior of fluid pressure when the containers were subdivided by one or more elastic-walled compartments.

In an attempt to answer these questions I have made a series of observations in order to determine whether or not the law of hydrostatics of Pascal applies to the living abdominal cavity with its fluid-containing hollow viscera, and also to determine the pressure relations in the abdominal cavity in those cases in which a true traumatic rupture of a viscus did occur.

Pascal's law is as follows: "Pressure applied from without to an enclosed fluid (liquids and gases) is transmitted equally in all directions without loss, and acts with equal force on all surfaces." This law applies to fluids within a single enclosure. No information could be found regarding the application of this law in enclosures subdivided into compartments by elastic membranes. To determine the pressure relations in such a system of fluid containers was the object of this study.

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In order to visualize more clearly the changes that took place in the interposing membranes during changes in pressure, experiments were made with apparatus consisting of glass and rubber before experiments were made on living dogs.

## EXPERIMENTS

EXPERIMENT 1.—A hole was made in the side of a florence flask by means of a blow torch. This hole was enlarged by heat, and a flange was formed about its edge. Over this opening in the flask a sheet of rubber tissue was fastened so that it was air-tight and water-tight (fig. 1 *a*, *B*). The mouth of the flask was closed by a rubber stopper containing two perforations through which glass tubes were inserted. One tube that entered the flask remained open. The second tube was attached to a rubber finger cot by a water-tight connection (fig. 1 *a*, *A*). The external ends of the tubes connected with U-shaped mercury manometers. The

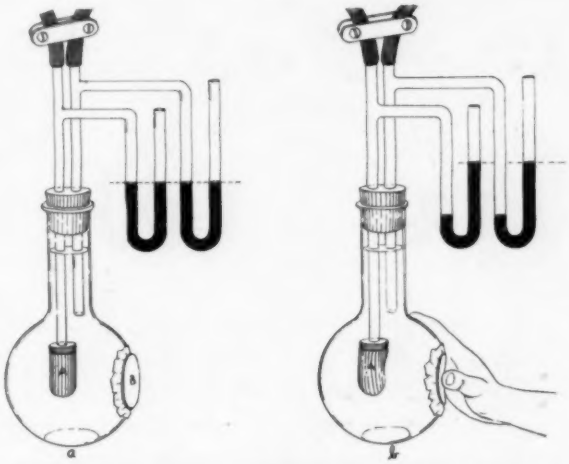

Fig. 1.—Diagrammatic representation of experiment 1.

sac (*A*) was filled with water and the flask was filled with water nearly to the top. In the assembling of the apparatus by insertion of the stopper into the neck of the flask there was some compression of fluid in the system, and the mercury rose in both manometers to an equal degree. In order to start the observations with the enclosed fluids at atmospheric pressure, a T-tube was interposed between the flask and the manometers. To this was attached a short rubber tube that could be opened or closed by a metal clamp. The completed apparatus is shown in figure 1 *a*. It can be assumed that the body of the flask represents the abdominal cavity. The rubber diaphragm (*B*) represents an elastic flexible portion of the abdominal wall. The finger cot (*A*) represents the stomach or any intra-abdominal hollow organ.

*Observation 1.*—Pressure on the rubber diaphragm (*B*) caused the mercury to rise to an absolutely equal degree in both manometers (fig. 1 *b*). A slight pressure caused a slight rise, and a greater pressure, a greater rise, but the rise was always equal. The equal rise in both manometers, however, was not in direct proportion to the degree of pressure on the diaphragm (*B*). The reason for this is that it

takes a certain amount of pressure to overcome the elasticity of the rubber diaphragm, and this pressure was deducted from the pressure exerted on the enclosed fluids.[1]

As all degrees of pressure on the diaphragm (*B*) caused an equal rise in both manometers, it was demonstrated that pressure on the outer surface of the sac (*A*) was equal to the pressure on its inner surface, and it was also demonstrated that the law of Pascal holds good in a closed system with an intervening elastic membrane.

*Observation 2.*—Pressure on the diaphragm (*B*) caused a dimpling in the wall of the sac (*A*) due to a displacement of fluids in both the flask and the sac.

*Observation 3.*—Tests were made with the apparatus containing air alone, with the apparatus completely filled with water, and with various proportions of air and water both in the flask and in the sac (*A*). In all combinations of air and water, pressure on the diaphragm (*B*) caused an equal degree of pressure in both manometers.

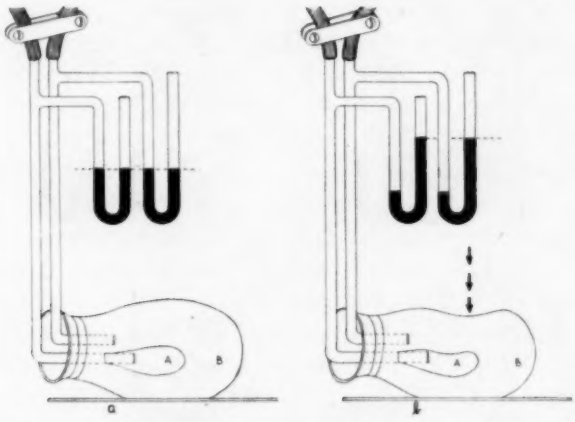

Fig. 2.—Diagrammatic representation of experiment 2.

*Observation 4.*—The rubber sac (*A*) was replaced by a 2 foot (60.9 cm.) piece of Penrose rubber tubing which was closed at its distal end. This lay coiled on the bottom of the flask, or the coils floated on the enclosed water, depending on the proportion of air and water in the two cavities of the system. All air, all water and various proportions of the two were tested, and in all instances pressure on the diaphragm (*B*) caused an equal rise in both manometers.

*Observation 5.*—Pressure on the diaphragm (*B*) caused no visible movements on the rubber tube replacing (*A*). It was known that with pressure on the diaphragm (*B*) there was a displacement of fluids as shown by the dimpling of the sac (*A*) in figure 1 *b*, but in the case of the long rubber tube this displacement of fluid occurred in a much larger volume of fluid, so that any dimpling or shrinking in the size of the tube was imperceptible.

1. This fact was determined by means of a similar apparatus, but with the rubber diaphragm in a horizontal position so that the pressure could be applied by means of graduated weights.

EXPERIMENT 2.—In this experiment the glass flask was replaced by a rubber bag in order that the conditions in the abdomen might more nearly be approached. In figure 2 *a* a rubber hot water bottle (*B*) represents the abdomen and the rubber bag (*A*) represents the stomach or other intra-abdominal hollow viscera. The attachment of this apparatus to the mercury manometers was similar to that shown in figure 1.

*Observation 6.*—All air, all water and various combinations of these fluids were placed in the two compartments of the apparatus, and in every instance pressure on the bag (*B*) caused an equal rise in the mercury of both manometers, as shown in figure 2 *b*. The hot water bottle being opaque, it was impossible to observe the sac (*A*), but it was felt that it must be dimpled on account of some displacement of fluids.

EXPERIMENT 3.—This experiment was made on a living dog. The operation was done under anesthesia with sodium amytal given intravenously. Through a midline incision the stomach was exposed. An incision was made in the stomach

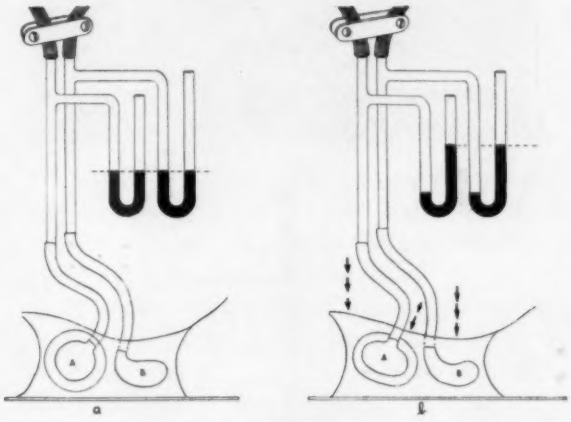

Fig. 3.—Diagrammatic representation of experiment 3.

just large enough to allow the introduction of a rubber balloon which had been filled with water without tension. The balloon was attached to a rubber tube, and about this tube the wound in the stomach wall was firmly sutured. When the stomach was opened it was found about half filled with solid and liquid food. This was not disturbed. Another rubber balloon was attached to a rubber tube and filled with water without tension. This was placed in the abdominal cavity among the loops of intestines to the right of the vertebral column. The abdominal wound was then sutured, making a firm closure about each tube at its exit. Each tube was then attached to the mercury manometers (fig. 3 *a*).

*Observation 7.*—Pressure was applied to each region of the abdomen, and the abdomen was compressed laterally; in every instance the pressure in the two manometers was equal (fig. 3 *b*).

*Observation 8.*—Blows on the abdomen directly over the stomach also caused an equal rise in both manometers, but no movements of the mercury could be observed that would indicate that the blow over the stomach caused a sufficient increase in the peristalsis of the stomach to lead to a rise in the intragastric pressure.

EXPERIMENT 4.—In the preceding experiment it was demonstrated that external pressure applied to the abdomen resulted in an increased intra-abdominal pressure which always equaled the intragastric pressure. In other words, any pressure on the abdomen caused an equal pressure on each side of the wall of the stomach. It would be impossible, therefore, to rupture a gastric ulcer by increasing the intra-abdominal pressure. However, if it took an appreciable amount of time for these two pressures to become equalized, an ulcer might rupture during this interval. When the movements of the columns of mercury in the manometers were observed, they appeared to rise simultaneously with the application of the pressure. However,

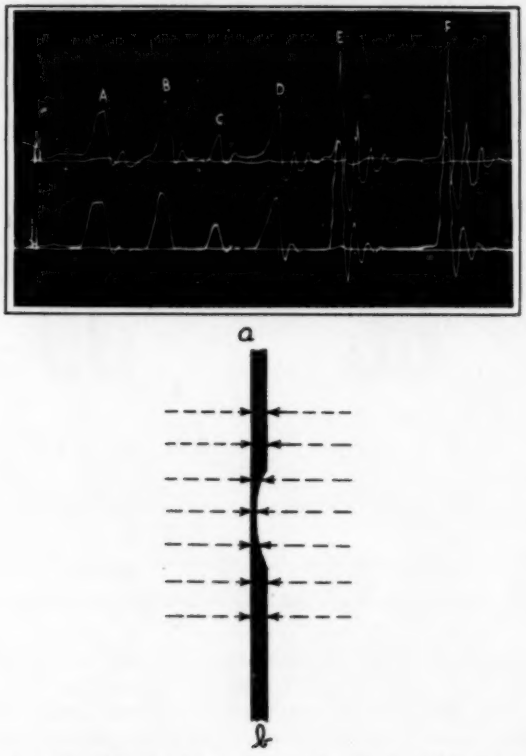


Fig. 4.—*a*, kymographic tracings in experiment 4; *b*, diagram showing equal pressure on both sides of a wall.

in order to obtain a more accurate record of the experiment, floats carrying a wire marker were inserted in the manometers. These markers, placed one directly above the other, recorded on a revolving drum the movements of the mercury.

The dog was prepared as in the preceding experiment. The anesthesia was very light, so that the dog responded to stimuli by the time the operation was completed.

*Observation 9.*—Figure 4 *a* shows the kymographic record of experiment 4. The upper curves are from the manometer attached to the stomach, while the lower curves record the pressures from the manometers attached to the balloon in the abdominal cavity. Before any pressure was applied a base line was run on the

revolving drum. This line was almost horizontal, the variations being due to the respirations.

Curves *A*, *B*, *C* and *D* resulted from various degrees of pressure on different parts of the abdomen. Curves *E* and *F* resulted from forcible blows on the abdomen with the fist. The intervening small curves are due to the elastic rebound of the rubber bags. This fact was determined by the exertion of different degrees of pressure on the rubber bags while they were outside the dog's abdomen but connected with the kymograph.

The foregoing experiments show from the kymographic record that pressure on the abdomen causing an increase in intra-abdominal pressure caused an equal and simultaneous increase in intragastric pressure.

*Observation 10.*—Forcible blows over the abdomen directly over the stomach produced no changes in the kymographic tracings that indicated additional changes in the intragastric pressure, the result of increased peristalsis.

From the foregoing observations it can be concluded that the law of Pascal applies to fluids in living elastic containers, and also that this law holds good when the container is subdivided by means of elastic partitions.

As the law of hydrostatics applies to the abdominal cavity of the dog and its contained stomach and as this law applies in a similar apparatus in vitro, it follows that it also applies to the pressure relations between the intra-abdominal cavity and all of the intra-abdominal hollow viscera. In other words, an increase in intra-abdominal pressure will cause an equal increase in the pressure in all of the hollow intra-abdominal organs, namely, the stomach, duodenum, small intestine, large intestine, appendix, gallbladder and urinary bladder, so long as their natural orifices remain closed. Therefore, it can be concluded that the wall of no hollow viscus can be ruptured by a simple increase in the intra-abdominal pressure, because the pressure on the visceral wall will be exactly equal on both sides (fig. 4 *b*).

From clinical experience, however, it is known that the hollow viscera do rupture under certain circumstances. With the exclusion of penetrating wounds, the causes of such ruptures may be grouped under three headings:

1. Diseases resulting in disintegration of the visceral wall. Common examples are the following: gangrene of the appendix, gangrene of a loop of bowel, a malignant growth on the wall of a viscus and progressive necrosis and ulcerations, such as gastric and duodenal ulcers, tuberculous ulceration of the bowel and ulceration secondary to calculi. In all of these conditions the rupture may be entirely spontaneous owing to the gradual dissolution of tissue; it may be aggravated by peristaltic waves in the adjacent visceral wall, or it may be hastened by the changes in pressure to be named later.

2. A hollow viscus may be ruptured by overinflation or over-distention. Such a condition is seldom seen unless the ruptured viscus is weakened by disease, as mentioned under group 1. In such a case the diseased viscus ruptures from overfilling and from overdistention with gases, the result of fermentation and putrefaction. A striking example of rupture from overinflation of a normal viscus is the rupture of the rectum or the large intestine following the so-called practical joke of placing the nozzle of a compressed air hose against the victim's anus.

3. Rupture of a hollow viscus may occur following external violence to the abdomen, such as severe blows or compression. The most com-

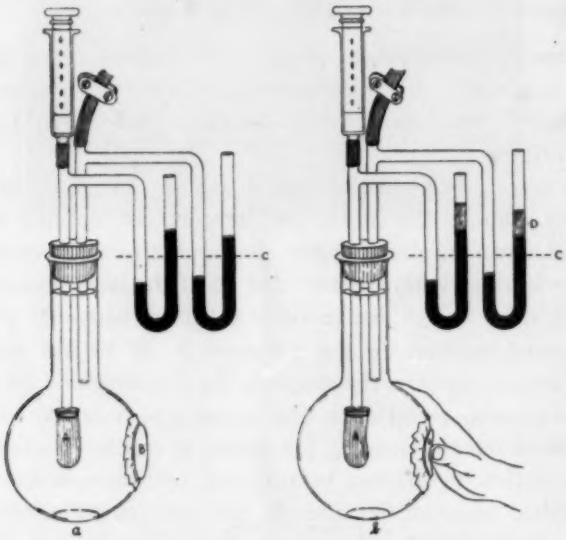


Fig. 5.—Diagrammatic representation of experiment 5.

mon example is the compression of the abdomen by the wheel of a vehicle.

In order to study the changes in intra-abdominal pressure in relation to the rupture of the hollow viscera, the following observations were made.

The first question to consider was the following: How would Pascal's law apply when one compartment in the system was raised to a higher pressure than that in the remainder of the system? It has been shown that the intra-abdominal and the intragastric pressure remain equal under ordinary conditions, but what would happen if there was an increase in the intra-abdominal pressure while the stomach was already distended with gas under pressure?

EXPERIMENT 5.—The same apparatus as shown in figure 1 was used, and a glass syringe was attached to the tube leading to the rubber sac (*A*). The mercury was allowed to settle to the same level in each manometer. The system was then closed, and by means of the syringe air was forced into the rubber sac (*A*) until it was distended under pressure.

*Observation 11.*—With the sac (*A*) distended the mercury rose in each manometer, but it rose higher in the manometer connecting with the sac (*A*) (fig. 5*a*). The line (*C*) indicates the normal level of the mercury. The reason that the pressure from the sac (*A*) is greater than that in the remainder of the system is because it takes a greater amount of pressure to distend the sac (*A*) than it takes to distend the diaphragm (*B*). With the apparatus as shown in figure 5*a*, if pressure is applied to the diaphragm (*B*), the mercury will rise in both manometers to exactly the same degree (fig. 5*b*, *D*); that is, the increment of rise in each manometer is always the same regardless of the amount of pressure applied to *B*.

This observation can be applied clinically as follows: If a patient is suffering from a gastric ulcer and the stomach is distended forcibly with gas or other fluid, but not forcibly enough to rupture the ulcer, and the patient by some means increases his intra-abdominal pressure, the relative pressure on each side of the ulcer remains the same. In other words, if the distention by gas or other fluids did not cause a rupture, an increase in intra-abdominal pressure would not cause a rupture.

*Observation 12.*—Similar tests were made with the two rubber bags as shown in figure 2*a*, and the same results were obtained.

This principle is not only true for the stomach, but for all of the intra-abdominal hollow viscera.

*Observation 13.*—By continued inflation of the sac (*A*) it can finally be made to rupture, but the pressure required is greater when the sac is in the closed apparatus than when the same type of sac is in the open air.

EXPERIMENT 6.—In this experiment the apparatus used consisted of two transparent balloons of different sizes, one placed inside the other. Each balloon was connected to a manometer. In this experiment the mercury manometers were rather difficult to handle; so the manometers from an apparatus for the determination of blood pressure were used. A T-tube was inserted between each balloon and the manometer to be used for inflation.[2] The assembled apparatus is represented by the solid lines in figure 6*a*.

*Observation 14.*—With the apparatus at rest both balloons assumed the spherical form, and the pressure in the external balloon (*B*) registered 20 while the pressure in the internal balloon (*A*) registered 40.

Pressure on the external balloon made it assume an oval form, and the pressure in each manometer rose to an exactly equal degree. In other words, pressure on the outer balloon caused an equal rise in pressure in the internal balloon, a phe-

2. In testing the degree of pressure required to inflate balloons of various sizes, it was found that the smaller balloons required a greater amount of pressure to inflate them to a moderate size than did the larger balloons. This difference is most probably due to the difference in the tensile strength of the two sizes of balloons. This has no bearing on the present problem, however, as this problem does not concern actual pressures but the relative changes in pressure following the application of external force.

nomenon exactly similar to that observed in figure 5. The pressure on both sides of the wall of the inner balloon was relatively the same no matter how much pressure was applied to the outer balloon so long as the walls of the outer balloon did not touch the walls of the inner.

*Observation 15.*—No matter how much the outer balloon was compressed or distorted, so long as it did not touch the inner balloon the inner balloon remained a perfect sphere and, as far as the eye could determine, did not change its size.

*Observation 16.*—When the pressure over the outer balloon was continued, the pressure in both balloons rose to the same degree, but as soon as the outer balloon was compressed to the degree that its walls touched the inner balloon and the shape of the inner balloon was in the least distorted or compressed, the pressure in the inner balloon immediately rose at a greater rate than the pressure in the outer. As the pressure continued, distorting both the outer and the inner balloon,

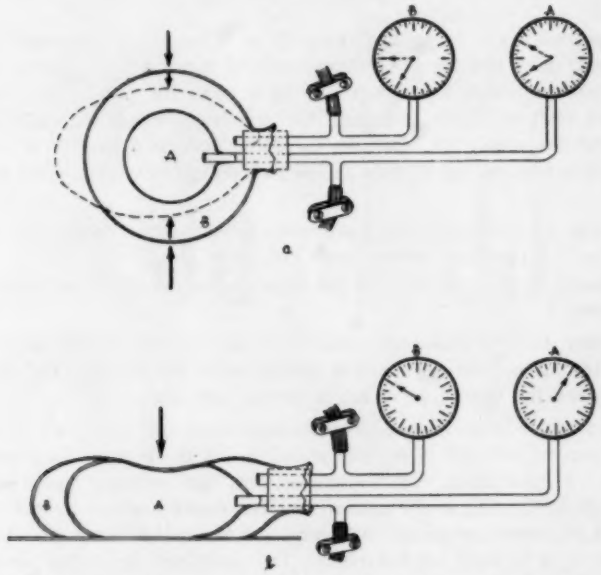

Fig. 6.—Diagrammatic representation of experiment 6.

the pressure in both manometers increased, but this increase in pressure was much more rapid in the inner than in the outer one. In fact, with this increasing pressure with distortion of both balloons, the increase in pressure of the inner compared to the increase in pressure of the outer balloon is approximately in the ratio of an arithmetical progression (fig. 6*b*).

When the pressure is continued over the inner balloon through the walls of the outer balloon, the inner balloon finally ruptures.

The experiments shown in figure 6 demonstrate that when one flexible elastic compartment is contained in another larger flexible elastic compartment, it is impossible to rupture the inner compartment by pressure on the outer until the pressure on the outer compartment is sufficient to compress or distort the outer compartment sufficiently to distort or compress directly the inner compartment. In other words, in order to rupture the inner compartment, the pressure must be applied directly to its walls with no interposing fluid. Again, for the inner com-

partment to be ruptured, it must be compressed sufficiently to produce internal pressure beyond its limits of elasticity in the same manner as if it were not surrounded with an outer compartment. The only difference in the rupture of the inner balloon as shown in figure 6 *b* and a similar balloon not inside a second balloon is that it takes a greater amount of pressure to rupture the inner balloon than a similar balloon in the open air.

## CONCLUSIONS

From the foregoing observations I believe that the following clinical conclusions can be deducted:

1. Anything that increases intra-abdominal pressure, such as muscular strains requiring the contraction of the abdominal muscles, coughing, sneezing, vomiting, blows or pressure exerted from the outside on the abdominal wall and distention of the abdominal viscera by either fluid or solid matter, tends to exert pressure equally over the entire abdominal wall, and if there are one or more points weaker than the rest of the abdominal wall, there will be a tendency toward the occurrence of hernia at these weakened areas.

2. The inflation or overdistention of a hollow viscus may lead to the rupture of that viscus if the internal pressure is sufficient to overcome the limit of elasticity of the viscus.

3. An increase in intra-abdominal pressure, such as is caused by muscle strains, pressure or blows over the abdomen, causes an instantaneous and equal increase in the pressure in the intra-abdominal hollow viscera, unless a viscus is distended to the point that its walls reach from the abdominal wall in front to the solid tissues on the posterior abdominal wall.

4. If an intra-abdominal hollow viscus is overdistended from within and there follows an increase in the intra-abdominal pressure, the relative pressure on both sides of the wall remains the same.

5. To cause rupture of any intra-abdominal hollow viscus by external force or pressure, this viscus must be distended so that its walls reach the opposite sides of the abdominal cavity, and the blow, force or compression must be directed over the distended viscus.

In other words, for rupture of a normal or a diseased stomach to be produced by violence, the stomach must be distended so that it can be compressed between the anterior abdominal wall and the vertebral column or between the lateral surfaces of the abdomen, and the direction of the violence must be directly over the stomach.

In order to produce rupture of the urinary bladder, it must be distended so that it can be compressed between the abdominal and pelvic walls, and the line of force must be directly over the bladder.

The same holds true for the small intestines, except that these tubes are often empty or are emptied by the abdominal force, in which case

the intestines may be crushed between the anterior abdominal wall and the bodies of the vertebrae in the same manner that a solid organ may be crushed.

The appendix, either normal or diseased, acts similarly to other intra-abdominal hollow organs. It is inconceivable that an appendix could in any way be affected by any increase in intra-abdominal pressure, such as strains, blows or compressions, unless there were a distended appendix superimposed by a mass of solid adhesions that extended to the anterior abdominal wall.

In order, therefore, for an intra-abdominal hollow viscus to be injured or ruptured it must be subjected to the same force that would be required to rupture it if the entire anterior abdominal wall were removed.

In the case of external hernial sacs in the abdominal wall, an increase in the intra-abdominal pressure will tend to force abdominal contents into these empty sacs, owing to the fact that the pressure on the outside of the sac is less than the intra-abdominal pressure on the inside. But internal hernias cannot result from increased intra-abdominal pressure, and loops of intestines, the appendix and other structures cannot be forced under bands or through apertures, because according to Pascal's law the pressure is equal in all directions, and any pressure, no matter how applied, would have the same tendency to push the structure or organ away from the aperture as to force the organ toward the aperture.

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